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General Summary

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The important surgical problem of peritonitis has held the attention of hosts of clinicians and laboratory investigators for many years, and the reports of their observations are abundant. The publications of the last few years bear witness to the fact that there are today many workers in the field of investigation of this disease. Nevertheless, we make no apology for joining them in an effort to elucidate this problem further, for the disease is the *bête noir* of the abdominal surgeon and yearly takes its heavy toll of life. We believe that any presentation of accurate observations, if correlated with the observations of others, will help in the eventual solution of the problem.

Peritonitis has been studied from many different angles. Clinical observations of the varied manifestations of the disease were, of course, the first to be reported. Later, anatomic and physiologic features were disclosed. With the advent of bacteriology, peritonitis offered a wide and bewildering field of research, as indicated by the numerous reports of studies made in the last decade of the last century and in the first decade of the twentieth. Of recent years, the chemical aspects of the disease have been intensively studied, and there has been a growing knowledge of the profound disturbance of chemical balance that takes place during the progress of this disorder, particularly when it is complicated by intestinal obstruction. Of late also, there has been renewed interest in the immunologic and serologic factors that play a part in the recovery from this grave disease and in the prevention of its development.

About five years ago, we elected to attack the problem from the immunologic and serologic side but we felt that to do so intelligently we should first have to review the older studies in bacteriology and make certain preliminary bacteriologic observations of our own to see if the more recent methods of bacterial cultivation, particularly of the anaerobic organisms, would yield results fundamentally different from those already reported. We spent some time, therefore, developing the technic of anaerobic culture and studying the pathogenic anaerobes which have received so much attention from bacteriologists since the World War. We have studied particularly the intestinal organisms of man and laboratory animals, both aerobic and anaerobic and those found in raw "catgut," because of the frequency of perforation of the intestine as an antecedent to the development of peritonitis.

The earlier studies of the bacteriology of peritonitis were made with an imperfect understanding of the requirements for growth of the anaerobic bacteria. The simple methods and even some of the elaborate methods that were used were not adequate to bring to light anaerobes that were frequently seen on smear, but not cultivated, and it is not surprising that at first emphasis was placed on the more easily growing organisms. The literature on this subject is voluminous. It would not

be profitable to attempt a complete compilation of the published reports, but, in order that we may compare our own results with those previously set forth we shall review briefly those articles which seem to us to be representative of the best work that has been done in this field

LITERATURE

In 1879, Grawitz¹ reported his studies in peritonitis, pointing out that there was a group of primary infections of the peritoneum and another group that was secondary to other lesions on the one hand, those which seemed to arise as a disease entity of the peritoneum itself and, on the other, those which developed by contiguity from disease of the intra-abdominal organs

Pawłowsky was among the first to study peritonitis experimentally, and reported his work in 1887² He injected croton oil and found that it produced a hemorrhagic exudate Trypsin produced a high degree of inflammation and even 0.25 Gm caused death in experimental animals Contents of the small intestine injected into the peritoneum produced a fibrinopurulent peritonitis from which he cultivated a small bacillus When this was injected in pure culture, death or recovery depended on the dosage If intestinal contents were filtered, the filtrate would not kill, or if it was sterilized by heating on eight successive days at 55 C, it had no effect Pawłowsky concluded that the intestinal bacteria were the prime factors in peritonitis, and the chemical ferments played a secondary rôle

In 1890, Bonnecken³ made a bacteriologic study of the sac fluids in cases of strangulated hernias He observed eight human cases and a series of experimental cases in dogs in which he produced an analogous lesion by passing a loop of intestine through a rubber ring and covering the loop with a rubber bag This was replaced in the abdomen and examined after given periods of strangulation or after death If it was examined within from twelve to eighteen hours the fluid was usually clear, if the strangulation was particularly tight or the duration longer, the fluid was found to be blood-tinged or dark brown, turbid and flocculent The appearance of the wall of the intestine varied from light venous hyperemia to hemorrhagic infiltration or frank necrosis Bonnecken made cultures, not only of these fluids,

1 Grawitz P Statistischer und experimentell-pathologischer Beitrag zur Kenntnis der Peritonitis, *Charité-Ann* **11** 770, 1886

2 Pawłowski A D Beiträge zur Aetiologie und Entstehungsweise der akuten Peritonitis, *Centralbl f Chir* **14** 881, 1887

3 Bonnecken H B Ueber Bakterien des Bruchwassers eingeklemmter Hernien und deren Beziehung zur peritonealen Sepsis, *Virchows Arch f path Anat* **120** 7 1890

but of the contents of the strangulated loops and the wall of the intestine as well. He found that the organisms in the fluid could also be found inside the intestine, and concluded that they passed through the wall. In several of these cases, including one human case in which the strangulation had lasted only four hours, the wall of the intestine showed only a high degree of venous hyperemia, and yet the fluid contained numerous bacteria. He found *B coli* in eleven of fifteen cases and other bacilli which he briefly described but did not name. There were also several different kinds of streptococci and staphylococci. No anaerobic cultures were made, and it is probable that even in mixed cultures he failed to observe any anaerobes. He felt that his cases clearly showed that there did not need to be very great changes in the wall of the intestine for the intestinal bacteria to pass through.

A year later, in 1891, Malvoz⁴ reported a study of peritoneal exudates at autopsy, and said that he agreed with Laruelle⁵ that peritonitis of intestinal origin should not be attributed to any organism except *B coli*. Malvoz found it in pure culture in a case of perforated gallbladder, in a case of perforated ulcer of the stomach and in a case of obstruction of the rectum without perforation. It was combined with other organisms in a case of mesenteric thrombosis with gangrene and in a case of perforated typhoid ulcer. Malvoz thought that it could not be considered a secondary invader, because it is so rarely found as a contaminant in cases of streptococcus or pneumococcus peritonitis. Laruelle found *B coli* in pure culture in two cases of perforated appendix. When he injected *B coli* into animals, he found that he could produce peritonitis, but that the lesion was more like that in human beings if he injected bile or sterile intestinal fluid along with the organisms. Laruelle, and Malvoz both agreed, however, that *B coli* is often present without perforation, and therefore the intestinal fluid is not necessary for the production of peritonitis. The question arises: do we know that intestinal juices do not pass through an inflamed wall as well as bacteria?

De Klecki,⁶ recognizing the intestinal origin of the organisms found in peritonitis, vouchsafed the opinion that the intestinal bacteria increase in virulence before or as they enter the tissues of the wall of the intestine. As time went on various workers added to the list of

4 Malvoz, E. Le bacterium coli commune comme agent habituel des peritonites d'origine intestinale. Arch de med exper et d'anat path **3** 593, 1891.

5 Laruelle, L. Etude bacteriologique sur les peritonitis par perforation, Cellule **5** 61, 1889.

6 de Klecki, C. Recherches sur la pathogenie de la peritonite d'origine intestinale. Etude de la virulence du colibacille. Ann de l'Inst Pasteur **9** 710, 1895.

bacteria found in peritonitis Jalaguier⁷ added *Staphylococcus albus*, Fraenkel⁸ added streptococcus, and Barbacci,⁹ pneumococcus. Each one stressed the importance of the organism observed by him, and although *B. coli* was generally found, its significance was questioned because of its apparently benign state within the intestine.

The first comprehensive report from the earlier workers was the result of observations by Tavel and Lanz,¹⁰ who, in 1893, carefully studied seventy-two cases and tried to correlate to some degree their clinical and bacteriologic observations. Although their methods were not adequate to recover many of the anaerobic bacteria, some of their observations are of particular interest and have been repeatedly confirmed. They divided their cases of peritonitis into five groups: (a) cases following lesions of the gastro-intestinal tract, (b) those following lesions of the gallbladder and liver, (c) those following lesions of the genito-urinary tract, (d) those following operative peritonitis and (e) those of hematogenous origin. They considered twenty-three cases yielding no bacteria on culture to be due to chemical irritants. Of the other forty-nine that yielded bacterial growth, fourteen gave a pure culture of a single species. The other thirty-five were "polymicrobial." *B. coli* was found in thirty of the forty-nine cases, and some form of streptococcus in twenty-eight. They distinguished three different forms of streptococci. No organisms similar to *B. aerogenes-capsulatus*, which had been reported the previous year (1892) by Welch and Nuttall,¹¹ were described. They found the cases with a single organism to be very diverse in nature while the polymicrobial cases came largely from intestinal lesions. In the mixed infections they found it difficult to say which organism was the most important. When no organisms were present, the prognosis was good, and in the cases in which organisms were found, the polymicrobial infections gave a better outlook than the monomicrobial, but they could not find any correlation between the severity of the clinical symptoms and the number of species found in any given case. They observed that lesions of the small intestine were much more dangerous than

7 Jalaguier M. Resultats de l'examen bacteriologique du pus d'une peritonite generalisee par perforation de l'appendice ileo-coecal, Bull et mem Soc de chir **18** 390, 1892.

8 Fraenkel, E. Zur Aetiologie der Peritonitis, Munchen med Wchnschr **37** 23, 1890.

9 Barbacci, O. Ueber Aetiologie und Pathogenese der Peritonitis durch Perforation Centralbl f allg Path u path Anat **4** 768, 1893.

10 Tavel, E. and Lanz O. Ueber die Aetiologie der Peritonitis, Mitt a d Klin u med Inst d Schweiz **1** 1, 1893.

11 Welch, W. H., and Nuttall G. H. A Gas Producing Bacillus (*B. aerogenes capsulatus* nov. spec.) Capable of Rapid Development in the Blood-Vessels After Death. Bull Johns Hopkins Hosp **3** 81 1892.

lesions of the large intestine and offered as a probable explanation that if perforation takes place in lesions of the small intestine, the contents of the intestine are so fluid that they spread around rapidly while the more solid contents of the large intestine are more apt to localize, to be less widely diffused

Flexner,¹² in 1898, reported a postmortem bacteriologic study of one hundred and six cases of peritonitis. While he admitted the possibility of error because of postmortem invasion, he thought that this was inconsiderable. Postmortem reports have the further disadvantage that there is no consideration of those cases in which recovery occurred. So that whereas Tavel and Lanz in studying specimens from the operating room found twenty-three that yielded no bacteria and that they called cases of "chemical peritonitis," Flexner found very few that yielded no growth and thought that "chemical peritonitis" must be an extremely rare condition. He divided his cases into twelve primary and ninety-four secondary cases. The primary cases were mostly terminal infections in patients with various and sundry chronic disorders. The secondary cases he divided into thirty-four exogenous and sixty endogenous. In the exogenous group, he placed operative infections in wounds as well as traumatic genito-urinary lesions and found that the bacteria in these cases corresponded to those usually found in wound infections, twenty-five of them yielding a single species and only nine more than one species. Of the sixty endogenous cases, two yielded no bacteria, twenty-one gave a single type of organism and thirty-seven gave multiple species. Of the thirty-seven multiple, thirty-four yielded two species, two had three species and one had four. "Anaerobic cultures were only made in exceptional cases"—he does not state why. And this is the more surprising because Flexner was associated with Welch in his studies with *B. aerogenes-capsulatus* and in 1896 reported cases of peritonitis yielding this organism. In Flexner's series *B. aerogenes-capsulatus* (*C. welchii*) was found only seven times. He brought out the fact that streptococci are much more common than staphylococci in cases of peritonitis of intestinal origin, but concluded that of all the organisms found, *B. coli* was the organism of greatest importance.

The reports thus briefly summarized represent the early observations that constitute the aerobic era of the bacteriologic knowledge of peritonitis. In 1896, a new epoch began when Welch and Flexner¹³ reported seven cases of peritonitis yielding *B. aerogenes-*

12 Flexner, S. The Etiology and Classification of Peritonitis. Philadelphia M J 2 1019 1898

13 Welch W H and Flexner S. Observations Concerning the Bacillus aerogenes capsulatus, J Exper Med 1 5, 1896

capsulatus We are not sure whether these are the same seven that Flexner later reported in his large group, but appearing together as they do in the earlier report, they constitute the first series of cases that suggested the importance of the anaerobic bacteria in this disease. They found the organism in five perforative lesions of the intestine and in two nonperforative lesions. Two years later in 1898, Veillon and Zuber¹⁴ came out as the champions of the anaerobic hypothesis. They examined the exudate in twenty-two cases of appendicitis. They found anaerobes in twenty-one of these cases, twice in pure culture, and from their observations drew these conclusions:

Anaerobes are constantly found in the pus of appendicitis, in abscesses around the cecum, and in the peritoneal cavity in general peritonitis. Their extreme abundance on smear, (?) their predominance over *B. coli* and other aerobes, and their existence in pure culture in certain of these cases, their pathogenic properties and chemical properties permit us to state that they play the principal role in the production of appendicitis. Due to their gangrenous properties, some perforate the appendix and some give typical gangrenous pus. It is their toxins which give the symptoms to which patients often succumb.

They described five different kinds of anaerobic bacilli, among them *B. perfringens* (which was later identified as *B. aerogenes-capsulatus* and has since been named *C. welchii*) and an anaerobic coccus. This report obviously ignored the aerobic organisms in order to emphasize the anaerobic and it called attention in a very emphatic manner to their presence even though it went farther than the evidence indicated in estimating their importance.

In 1902, Friedrich¹⁵ reported a study of perforative peritonitis in which both aerobes and anaerobes were described. *B. coli*, streptococci, *B. proteus*, *B. pyocyaneus* and staphylococci were found among the aerobes. Anaerobes were isolated from almost every peritoneal exudate. He does not describe them further than to say that the bacilli were generally of the malignant edema or tetanus types and that there were also anaerobic streptococci. Thus Friedrich confirmed to some degree the work of Veillon and Zuber and at the same time recognized the rôle played by the aerobes although he failed to give statistics and did not clearly indicate his opinion of their relative importance.

In 1904 Lanz and Tavel¹⁶ having had the anaerobes called to their attention by reports that followed their earlier one¹¹ published another

14 Veillon and Zuber. Recherches sur quelques microbes strictement anaerobies et leur rôle dans la pathologie humaine. Arch. d. med. exper. et d'ant. path. 10: 517, 1898.

15 Friedrich, P. L. Zur bakteriellen Aetiologie und zur Behandlung der diffusen Peritonitis. Arch. f. klin. Chir. 68: 524, 1902.

16 Lanz, O. and Tavel, F. Bacteriologie de l'appendicite. Rev. de chir. 30: 43 and 215, 1904.

series in which they compared the bacteriologic flora found in the contents of normal appendixes, diseased appendixes and appendiceal abscesses to see whether there was any correlation between the bacterial content and the pathologic state. In this report they differentiated between *Streptococcus pyogenes* and the other intestinal streptococci. They also subdivided the anaerobes, giving the bacillus of malignant edema and the pseudotetanus bacillus the most important places numerically. They included in the malignant edema group *B. perfringens* of Veillon and Zuber and *Vibrio septique* of Pasteur. Their group of normal appendixes was small, only eight specimens being studied, whereas there were one hundred and thirty-eight diseased appendixes. In the normal appendixes, *B. coli* was found in 100 per cent, *Streptococcus pyogenes* in 25 per cent, diplostreptococci in 37.5 per cent, malignant edema bacilli in 62.5 per cent and pseudotetanus in 45.4 per cent. Over 10 per cent of the diseased appendixes yielded no growth. Thus they thought to be due to the emigration of leukocytes and the phagocytosis of the bacteria. They stated:

The qualitative analysis confirms our ideas. One would expect to find more pathogens and less saprophytes in the pathologic appendixes than in normal. It is seen that the streptococci and diplococci are increased, while the coli, the malignant edema, and the pseudotetanus groups are less, but as there was no way of determining the virulence of these organisms for man, we cannot draw any definite conclusion.

In spite of these reports of anaerobes as factors in the disease, a number of later observers published the results of studies that minimized the anaerobes or ignored them entirely. It is quite evident that they either made no effort to find them or that their technic was not adequate to recover them. For example, in 1903, Manahan,¹⁷ who studied nineteen cases of peritonitis to determine the presence of bacteria in the fibrin clinging to the wall of the inflamed intestine, made smears of the exudate and cultivated it. In three cases he saw organisms resembling *B. aerogenes-capsulatus* of Welch in the smear and in the fibrin, but they failed to grow with "Wright's anaerobic method." Later, in 1905, when Manahan reported a bacteriologic study of a series of one hundred and ten cases of peritonitis at autopsy, he included only one case that yielded the Welch bacillus. He emphasized the importance of the streptococci, for he found them in pure or mixed culture in fifty-four of the eighty-nine cases in which a bacteriologic examination was made while *B. coli* was present in only forty-five.

¹⁷ Manahan, T. J. Bacteriology of the Fibrinous Exudate in Septic Peritonitis. J. M. Research 9:445, 1903. The Bacteriology of General Peritonitis, Boston M. & S. J. 152:346, 1905.

necessity for adequately controlling results of this kind with normal persons, is obvious. This was not done adequately by Kotzenberg.

In 1911, Heyde²² published an excellent article based on clinical observations and painstaking laboratory studies. He reviewed the literature up to that time thoughtfully and critically and appears to have had a clear understanding of the whole problem. He obtained material for bacteriologic examination from one hundred and two patients. The lesions were classified as those of purulent appendicitis, gangrenous appendicitis, peritonitis of appendical origin, abscess and interval or chronic appendicitis. He examined by smear and culture the contents of the removed appendixes, the peritoneal exudates and in a few cases the pus from secondary abscesses. He showed the correlation of the bacteriologic observations of the different fluids in the individual cases but made no effort to correlate these observations with the clinical course of the disease. His clinical groups overlap to a considerable degree, particularly in the gangrenous appendicitis, peritonitis and abscess groups. It is not clear which of his patients had perforative lesions and which did not. He stated that most of the lesions were perforative. Furthermore, in his tables he did not distinguish between the flora of the contents of the appendix and of the peritoneal exudates. By going through his case reports and selecting the results of his study only with regard to the peritoneal exudates, which seem to us to be infinitely more important than the contents of the appendix, we have been able to obtain data that we can compare with our own, particularly with regard to the bacteriologic studies. Heyde was manifestly in search of the anaerobes. He used the methods of von Hibley and others of his own which were chiefly designed to avoid the prolific growing propensities of *B. coli*, which was so commonly present that it gave him all sorts of trouble. He depended chiefly on dilution tube cultures in solid or semi-solid mediums. Even though it was by far the most frequent organism found, Heyde considered that *B. coli* played a subordinate rôle in the etiology of appendicitis. Of considerably more importance, in his opinion is the small gram-negative nonspore-forming anaerobic organism *B. thetoides*, which is the same as Veillon's and Zuber's *B. fragilis*. He could not demonstrate its pathogenicity. He found it difficult to separate this bacillus from *B. coli* in the undiluted specimens, but by diluting them down through a series of agar tubes, which solidified after seeding, he was able after incubation to pick out the colonies of this organism. In the forty-nine peritoneal exudates that he examined, he found *B. thetoides* in about 45 per cent and *B. coli* in about 60 per cent. He

²² Heyde M. Bakteriologische und experimentelle Untersuchungen zur Ätiologie der Wurmfortsatzentzündung (mit besonderer Berücksichtigung der anaëroben Bakterien). Beitr. z. klin. Chir. 76:1 1911.

found *B. acrogenes-capsulatus* (*C. welchii*) in about 15 per cent, while other spore-forming anaerobes, which he classified as bacilli of the malignant edema and of the pseudotetanus groups, were present to a lesser degree. Certain nonspore-forming, gram-positive rods (*B. ramosus* and *B. ramosoides*) were present in from 15 to 25 per cent, and several of these were found in pure culture. An organism which he called the parapneumococcus was present in almost 25 per cent of his cases, while anaerobic streptococci were found in 20 per cent of the cases. Heyde's experiments on animals were limited in number, and although he found them to be consistent, his results were not sufficiently striking to repeat here. His final conclusions with regard to the clinical cases were as follows:

- 1 The anaerobic organisms, in all stages of appendicitis and the peritonitis arising from it occur in the greatest variety and number.

- 2 They invade the peritoneum more quickly than the aerobes and spread themselves over the serosa without being accompanied by the aerobes.

- 3 There seem to be particular kinds of organisms present in particular conditions of infection which have a particular etiologic significance.

In going over his results, it does not seem to us that Heyde is justified in making these sweeping statements. We feel that his interest in the anaerobes led him not to give full credit to the aerobes. Heyde's results differ from the ones that we shall report, chiefly in the incidence of the small gram-negative anaerobic bacillus, *B. thetoides*, which we found in only three cases. On the other hand, his incidence of *B. coli* is low compared with ours, particularly as his cases were largely perforative. We found *B. coli* in almost every instance with a perforative lesion. While it is conceivable that this prolific gram-negative anaerobic *B. coli* may easily hide the slower growing gram-negative anaerobic *B. thetoides*, it does not seem likely that the anaerobe would be confused with *B. coli*, nor does it seem likely that these organisms would be mistaken for one another when they were once isolated. Therefore, we must grant that Heyde's results are probably accurate for his series and we shall endeavor to evaluate the importance of this organism in our further studies.

In 1912, Fishbein²³ reported some postmortem bacteriologic studies which largely confirm the previous work by Manahan and by Flexner and although he refers to Heyde and other students of the anaerobic organisms, he states that anaerobic cultures were usually not made in his series.

²³ Fishbein, M. Contribution to the Bacteriology of Peritonitis with Special Reference to Primary Peritonitis, *Am. J. M. Sc.* **144**: 502, 1912.

Wilkie,²⁴ in 1912, emphasized the advisability of the surgeon examining microscopically in the operating room smears from the peritoneal fluid in cases of diffuse peritonitis in order to have a basis for deciding the question of drainage and for making a prognosis in any given case. His belief was that if the polymorphonuclear leukocytes showed active phagocytosis, and particularly if these cells were found ingested by macrophages, recovery was assured and drainage was usually unnecessary. Wilkie believed that this was more important than cultural studies because of the time required to complete them.

In 1915, Carslaw²⁵ carried this idea further and went into fine distinctions of cellular differentiation and into the question of cellular disintegration. Carslaw, in general, confirmed Wilkie in the matter of phagocytosis, but said that he thought phagocytosis of bacteria was more important than phagocytosis of cells. He believed that the duration of the disease had to be considered, for example, the absence of polymorphonuclears early in the course of the disease was not surprising, but if absent late in the course, the prognosis was bad. On the other hand, early degeneration of polymorphonuclears was bad and late degeneration was to be expected. Carslaw did not agree with Wilkie that the smear could give a basis for drainage, because that depended rather on the presence or absence of necrotic tissue.

Of recent years there have been only two reports that warrant particular mention. One of these by Brutt,²⁶ in 1923, emphasizes the anaerobic streptococci. It seems likely that he included in this group certain micro-aerophilic streptococci that were not really anaerobes but which in the first few artificial transfers behaved as such. He considered without convincing proof that the anaerobic streptococci tend to produce thrombophlebitis, and thus bacterial gangrene and perforation.

In 1928, Weinberg and his associates²⁷ reported the results of studies carried out over a period of several years in the field of anaerobic bacteriology. During the war he was struck by the clinical similarity between cases in which the patients died of peritonitis following acute appendicitis and those in which they died of gas gangrene. He suspected that this was due to the rôle played by the anaerobes in both of these diseases.

24 Wilkie, D. P. D. Prognostic Value of an Immediate Examination of Peritoneal Exudates, *Internat. Clin.* **4** 145, 1912.

25 Carslaw, R. B. On the Character, Significance and Prognostic Value of Peritoneal Exudates, *Brit. J. Surg.* **3** 8, 1915-1916.

26 Brutt, H. Die Bedeutung der anaeroben Streptokokken für die destruktive Appendicitis, *Beitr. z. klin. Chir.* **129** 175, 1923.

27 Weinberg, M., Prevot, A. R., Davesne, J. and Renard, C. Recherches sur la bactériologie et la sérothérapie des appendicites aiguës, *Ann. de l'Inst. Pasteur* **42** 1167, 1928.

In referring briefly to the literature of the bacteriology of appendicitis, Weinberg spoke of the aerobic epoch and the anaerobic epoch and suggested that the pendulum has swung too far in giving the anaerobes almost exclusive responsibility in the etiology of appendicitis. Weinberg did not mention specifically the work of Heyde, though he doubtless knew of it. Weinberg's material, though more voluminous, was not as comprehensive as Heyde's, because the latter examined peritoneal exudates as well as appendical contents, while Weinberg did not.

Acute and gangrenous appendixes were sent to Weinberg's laboratory in sterile containers from various hospitals in Paris and were examined "usually the same day." They were placed in a Petri dish and with fine scissors opened from end to end and laid out flat. To quote from their report: "The pathologic exudate from the level of the lesion was sucked up into a sterile pipette, taking care to avoid fecal material and fecoliths so as to eliminate their flora and study exclusively the bacteriology of the specific lesions of acute appendicitis." This technic is subject to grave criticism, for it is inconceivable that it would be possible to avoid cultivating intestinal organisms that were only casually and not causally present at the site of the lesion on the interior of an appendix that had been opened from end to end. However, by passing this material through a series of dilutions of solidifying culture mediums to a point where, after incubation, individual colonies could be fished, those organisms which were present only in small numbers would largely be eliminated, and only those presumably most active at the site of the lesion would be recovered. One could not be sure, however, that the organisms in greatest number were necessarily causative or even active in the lesion. With these conditions in mind, one must discount to some degree the statistics which Weinberg and his co-workers present, and yet we believe that his results have considerable significance. Weinberg studied one hundred and sixty acutely inflamed appendixes, fifty-eight of which were gangrenous. He does not state how many of the gangrenous appendixes had perforated. From the material removed from these lesions he obtained pure cultures of single species in nineteen cases. This is surprising and is perhaps indicative of the efficacy of his technic. In 49 cases he found two species, in 47, three, in 23, four, in 16, five, in 4, six, and in 2, seven. Altogether there were 264 aerobes and 204 anaerobes. Of the aerobes, *B. coli* was found in 85 per cent of the cases. The enterococcus group was found in 30 per cent of cases while other aerobic bacteria occurred much more rarely. *B. parvum* (*C. welchii*) was found in 33 per cent of cases. Anaerobic gram-negative bacilli and anaerobic cocci were present in 39 and 19 per cent, respectively. Although the aerobes outnumbered the anaerobes in the whole series the anaerobes predomi-

nated in the gangrenous cases, and Weinberg concluded that the gangrene was due to their presence. He found the *B. coli* strains and the *C. welchii* strains to be pathogenic for laboratory animals, but the other frequent organisms, namely, the enterococci, the gram-negative anaerobes and the anaerobic streptococci were for the most part innocuous when injected in pure culture. In association with the others, however, his experiments seem to indicate that they either became pathogenic or enhanced the power of the associated organisms. Although he was handicapped by having no measure of the effect of the enterococcus alone and the results are therefore not conclusive, the experiments suggest that the symbiotic action of the organisms found in these lesions produce an effect which they cannot produce singly. Weinberg expressed the belief that the production of gangrene is largely a symbiotic effect of two or more organisms even though he was not able to demonstrate this conclusively. He did not indicate which of the anaerobes present beside *C. welchii* play a rôle in this symbiotic action, although he implicated the gram-negative bacilli because of their prevalence.

BACTERIOLOGIC METHOD

MATERIAL AND TECHNIC

It seemed to us more rational in studying peritonitis to examine the material actually present in the peritoneal cavity and presumably left behind, to some extent at least, after operation, rather than to examine either the contents or the wall of an organ that had been removed from the patient and was no longer a factor in his illness. We, therefore, centered our attention almost exclusively on the peritoneal exudate. The whole surgical staff cooperated with us in this study. Some of the patients were our own. Most of them, however, were under the care of other surgeons in our clinic, although one of us was frequently present at the operation as an observer. As soon as the peritoneum was opened and it was seen to have an excess of fluid, as much as possible was taken up in a sterile syringe. If the fluid was present in relatively small quantities, two sterile cotton swabs were saturated with the fluid. If the operation occurred during the day, these specimens were for the most part taken directly to the laboratory, if the operation had been performed at night, the specimens were placed on ice and examined in the morning. It was thought that the delay of a few hours before examination would make a great difference in the results of culture but such was not found to be the case. There was no appreciable difference between the day and night cultures. The specimens were sent or taken to the laboratory accompanied by a slip stating the duration of the symptoms, the diagnosis, the description of the fluid as to turbidity and consistency, quantity, location and odor, the description of the appear-

ance of the peritoneum and whether or not any perforation was present. In the large majority of cases, smears were made from the fluid before inoculation on glass slides for direct staining. When the specimens consisted simply of two saturated swabs, these were streaked directly on a pair of 5 per cent sheep's blood agar Petri plates and then broken off and a whole swab introduced into each of two cooked meat medium tubes containing 0.2 per cent dextrose and of p_H 7.6, one of which had been prepared to receive anaerobic cultures by preliminary boiling to drive off the contained air. When a large quantity of exudate was available, two meat tubes were inoculated with from 0.1 to 0.5 cc and a large drop smeared on the surface of each of two blood agar plates. One plate and one tube were then incubated aerobically and the others anaerobically in a modified McIntosh and Fildes jar²⁸. The tubes and plates were examined next day, but if there was no growth the incubation of negative cultures was continued for four or five days or longer. Occasionally, growth would appear in the second twenty-four hours and not in the first, but in our series, cultures that were negative after forty-eight hours remained so. When growth appeared on the plates, colonies were fished and identified in the usual way by morphologic and cultural studies. When the tubes showed growth they were plated and transfers made to fresh mediums in tubes which were heated to 70, 80 or 90 C, for fifteen minutes to destroy the nonspore-formers and qualitatively select the spore-formers. Colonies growing on the anaerobic plates were repeatedly plated both aerobically and anaerobically so as to determine their purity and their anaerobic requirements. We classified as anaerobes only those which would grow solely on the anaerobic and not on the aerobic blood agar plate after four or five transfers, except in the case of *C. welchii*, which can usually be identified after one or two transfers.

ADVANTAGES OF THE TECHNIC

We consider the anaerobic jar, with a replacement of the oxygen by hydrogen to be ideal for anaerobic cultures because with it any mediums that can be used aerobically may be used anaerobically. An indicator adequately checks the degree of anaerobiosis. Blood agar plates not only favor those organisms which require some enrichment of medium but permit the growth of the hemophilic organisms and signal at once the presence of the hemolytic bacteria. We are certain that all of the known pathogenic spore-forming anaerobes grow well on these blood agar plates, and we have made countless observations of their cultural characteristics on this medium. The blood agar plates served not only

28 McIntosh, J., and Fildes, P. A New Apparatus for the Isolation and Cultivation of Anaerobic Micro-Organisms. *Lancet* 1: 768, 1916.

to permit the growth of anaerobes but inhibited the exuberant growth of certain aerobes such as the gram-negative bacilli, which frequently overgrow other colonies aerobically. The 0.2 per cent dextrose cooked meat medium is particularly favorable for anaerobic as well as for aerobic organisms. The meat not only acts as a buffer, but contains peroxidase which permits certain strict anaerobes (e. g., *C. welchii*) to grow without sealing the medium or incubating it in the anaerobic jar. The strictest anaerobes, however, e. g., *C. novyi* (*B. oedematiens*) require the jar, and therefore in our study we always incubated the tubes in the deoxygenated environment. The meat medium is just as good as brain medium, for with putrefactive organisms the meat is attacked and becomes discolored. The direct inoculation of plates gives some idea of the relative numbers of viable organisms in the exudate, while on the other hand, the most prolific organisms soon predominate in the fluid cultures so that the plates made from the broth cultures give no indication of the relative numbers of organisms in the original specimen.

The cooked meat medium in every case received a heavier inoculation than the direct plates, and therefore, organisms were recovered frequently from the meat medium which did not appear on the first plates. The combined aerobic and anaerobic cultivation of each specimen, both on blood agar plates and cooked meat medium, and the later transfer from the cooked meat medium to other blood agar plates gave us several chances to recover both the aerobic and the anaerobic organisms in each case. On blood agar plates, the *C. welchii* colony is usually very easy to distinguish because of its outer zone of partial hemolysis. The results of the study as given below indicate fairly well, therefore, the occurrence of this anaerobe. *B. coli* is, of course, easily recovered because of its profuse growth and the large size of its colony. The streptococci, however, may frequently be missed, and the groups may be confused because of the variability of the size and the appearance of the colony, the property of methemoglobin formation and the anaerobic requirements. Some strains will grow only anaerobically on the first or second transplants, but will then grow aerobically. Some will grow on the blood agar plate without changing the blood for a generation or two and then will be frankly green. Many of the streptococci were green from the start and a few of these, after a number of transplants, became slightly hemolytic.

LIMITATIONS OF THE TECHNIC

Although we consider the foregoing technic adequate for the isolation of most aerobes and all of the well known pathogenic anaerobes, even those that require the strictest anaerobiosis we do not claim that

every species present in every peritoneal exudate was recovered. There may very well have been organisms that would not grow in any mediums that we used, and there may have been others the growth of which was inhibited by the presence of other species, or which were outgrown by them both on the plates and in the fluid mediums. By an examination of the thickest part of the growth on the plate as well as the isolated colonies, we were often able to demonstrate the presence of those slowly growing organisms if they were morphologically different from the organism which is overgrowing them. Then it was usually possible to isolate them by replating the culture. But organisms present in fewer numbers than the predominating organisms, if they were morphologically indistinguishable from them, may have been lost. For example, if a small gram-negative nonspore-forming anaerobic bacillus should be present in the same exudate with *B. coli* but in smaller numbers, it might be missed. If it were present in as great or greater numbers, the chances are greater that it would be picked up on the anaerobic plate which inhibits to a considerable degree the exuberant growth of *B. coli*. It is possible that our results do not adequately indicate the incidence of this group of organisms which Runeberg, Heyde and Weinberg found rather frequently. On the other hand, the spore-forming and the gram-positive organisms are not likely to be missed, and it is in this group that all of the anaerobic bacilli are found which up to the present are known to be pathogenic for man.

NOMENCLATURE

In this study we have aimed to make large bacterial groupings rather than to go into the minutiae of cultural variations which seemed to us to be without particular value. For example, we did not attempt to subdivide the *B. coli* group, although we observed that at least four of these subgroups were represented. With the streptococci, their variability on successive cultivation, as previously stated, made our division somewhat arbitrary, but it seemed worth while first to set apart the hemolytic group and the anaerobic group and then separate the green producing streptococci from the other nonhemolytic types. All small gram-positive rods were grouped together as aerobic diphtheroids while the larger gram-positive spore-forming aerobes fell into the *B. subtilis* group. Certain gram-negative aerobes, for example, *B. proteus* and *B. pyocyaneus* were fairly easy to separate from the *B. coli* group and were given their usual names.

The taxonomy of the anaerobic bacilli has recently been clarified by the persistent efforts of a number of workers, and the Society of American Bacteriologists has adopted the term *Clostridium* to denote the large group of anaerobic spore-formers. We have, therefore, used the

official term *Clostridium welchii* to denote the common gas bacillus, *B. aerogenes-capsulatus* of Welch or *B. perfringens* of Veillon and Zuber. The other pathogenic gas gangrene organisms, *C. oedematis-malignum* (*Vibrio septique*), *C. novyi* (*B. oedematiens*) and *C. oedematoides* (*B. sordelli*) were not found in our series, nor was *C. tetani*. The other oval central or subterminal spore-forming anaerobes, which were very few in numbers, have been placed in the *C. sporogenes* group, while the oval end spore-formers, have been placed in the *C. tertius* group. The gram-positive, nonspore-forming anaerobes have been grouped together as anaerobic diphtheroids, belonging in general to the *B. ramosus* group, while the gram-negative nonspore-forming anaerobes belong to the *B. fragilis* or *B. thetoides* group.

CLINICAL METHOD

In order to correlate the bacteriologic observations with the clinical course without bias, the records were examined and the data obtained from them at the end of the study and without reference to the bacteriologic results. Because of the emergency of operation in many instances, data which we would have liked to have were not on the clinical record. It was found that in some instances the absence of a specific symptom or sign probably meant that it was not present, for example, chill. In other instances it probably meant that it was not elicited, for example, "rebound tenderness." This must be kept in mind when the incidence of these symptoms or signs are considered. The symptoms that we thought might be of some significance were the following: nausea, vomiting, fever, chill, diarrhea, constipation and obstipation. In the cases of appendicitis, we were anxious to know whether or not the development of the disease was typical, by which we mean the rather sudden onset of general abdominal or epigastric pain localizing after a time in the right lower quadrant. The physical signs that we thought might be important were tenderness, rigidity, rebound tenderness, distention, mass, pelvic signs of tenderness or mass and the number of abdominal quadrants that were involved. The only laboratory examination considered for all cases was the white blood cell count. The severity of the case was judged from a consideration of the general appearance of the patient and the whole aspect of the case before operation. The operative observations with the pathologic diagnosis were recorded. The amount, character, location and odor of the fluid as described by the operator were noted. The procedure of the operator and the after-treatment, with particular reference to the use of serum, infusions or transfusions were listed. The development of complications or serious sequelae, the duration of the stay in the hospital, the age of the patient and the final outcome were recorded.

PRESENTATION OF DATA

The most obvious results of the clinical review of these cases was the necessity for a diagnostic classification. This perhaps requires a definition of terms used, in order that there may be no misunderstanding. By peritonitis, we mean an inflammatory reaction of the serous lining of the abdominal cavity either on the parietes or on the contained organs which results in an increase above the normal of the free fluid within the cavity and a loss of the normal smoothness, sheen and color of the membrane itself, with the deposition of fibrin on the surface. This may be a local process with or without an adherence of adjacent surfaces to form a limiting wall. The former we have called acute local peritonitis, the latter an abscess. If the process was not localized and the limits or boundaries were not evident, we have called the process acute diffuse peritonitis. A determination of the focus of the infection has been made without difficulty in all but eight cases. Five of these were abscesses in the right lower quadrant in which the appendix was not seen but was probably the source of the infection. One patient had a pelvic abscess which formed after the incidental removal of an appendix during an operation for another lesion. The cause of one fairly extensive acute diffuse peritonitis, thought at first to be of tuberculous origin, was and is still a mystery. In one case there was a diffuse peritonitis from a questionable perforation of the sigmoid diverticulum or an appendix epiploica. A summary of all the cases, according to these diagnoses, is given in table 1. It is seen that certain diseases frequently associated with peritonitis are absent from our series. This is chiefly because the genito-urinary and gynecologic departments are separate from the main surgical service. This explains the absence of cases due to rupture of the bladder, ureter, kidney or pelvis and the relatively small number of cases with tubal infection. The relatively common children's peritonitis of the pneumococcus and hemolytic streptococcus variety is likewise absent, possibly because of our rather limited pediatric service, although 12 per cent of our patients were less than 10 years of age. The only fulminating streptococcic case in our series occurred in an adult. Postoperative peritonitis is represented only by the three cases of volvulus. No doubt others occurred during the course of the study which did not come to operation. Thus it will be seen that these figures cannot be taken to show the proportional causes of peritonitis except so far as it is seen in a general surgical service. Under these circumstances, one is not surprised to find that about three fourths of the cases were due to acute appendicitis.

A summary of the clinical features and bacteriologic observations of the whole group simply give a confused mass of statistics which have little meaning. It is only when we divide them according to cer-

tain pathologic diagnoses that the important features of the study can be made plain, and sometimes it is necessary to subdivide still further and even to analyze the individual cases to bring out the most significant points. Although we hesitate to draw general conclusions from small groups of cases, a perusal of table 1 will give some indication of the relationship of certain lesions to the extent of peritoneal involvement, for example, the great majority of cases of acute appendicitis in which the lesions did not perforate or become gangrenous seem to be associated with acute local peritonitis rather than with acute diffuse peritonitis or

TABLE 1—*Pathologic Diagnosis in One Hundred and Six Cases of Peritonitis*

Acute appendicitis with acute local peritonitis	31	} 37	} 76
Acute appendicitis with acute diffuse peritonitis	4		
Acute appendicitis with abscess	2		
Perforated appendicitis with acute local peritonitis	2	} 30	
Perforated appendicitis with acute diffuse peritonitis	11		
Perforated appendicitis with abscess	12		
Perforated (?) appendicitis with abscess	5		
Gangrenous appendicitis, no perforation but acute local peritonitis	6	} 9	
Gangrenous appendicitis, no perforation but acute diffuse peritonitis	2		
Gangrenous appendicitis, no perforation but abscess	1		
Volvulus of ileum with acute diffuse peritonitis	2	} 10	
Strangulated hernia with acute local peritonitis	2		
Perforated duodenum with acute diffuse peritonitis	2		
Perforated jejunum with acute diffuse peritonitis	1		
Perforated ileum with acute diffuse peritonitis	3		
Volvulus of sigmoid with acute diffuse peritonitis	1	} 6	
Perforated colon with acute local peritonitis	1		
Perforated colon with acute diffuse peritonitis	3		
Perforated (?) colon with acute diffuse peritonitis	1		
Acute cholecystitis with acute local peritonitis	2	} 6	
Acute cholecystitis with acute diffuse peritonitis and pancreatitis	1		
Perforated cholecystitis with acute diffuse peritonitis	2		
Perforated cholecystitis with abscess	1		
Acute mesenteric lymphadenitis with acute local peritonitis	2	} 8	
Puerperal fever with acute diffuse peritonitis	1		
Puerperal fever with abscess	1		
Acute salpingitis with acute local peritonitis	1		
"Idiopathic" hemolytic streptococcic acute diffuse peritonitis	1		
"Idiopathic" unknown cause acute diffuse peritonitis	1		
"Idiopathic" unknown cause pelvic abscess	1		

abscess. The great majority of cases of perforated appendicitis seem to be associated with acute diffuse peritonitis or abscess in about equal proportions. Gangrenous appendixes which have not perforated are more likely to be associated with an acute local peritonitis than with an abscess or an acute diffuse peritonitis. Perforated lesions of the intestine seem to be associated with an acute diffuse peritonitis rather than with a localized process.

We shall present the results of our study from four different points of view: the pathologic diagnosis, the extent and nature of peritoneal involvement, the growth of organisms, the untoward results. In the tables, an attempt is made to show the correlation between the clinical course and the factors being considered. Only the more striking features are significant, and too definite conclusions must not be drawn.

from small groups of cases. The points which seem to us significant are indicated by an asterisk.

CONSIDERATION OF THE DATA FROM THE POINT OF VIEW OF THE PATHOLOGIC CONDITION

LESIONS OF THE APPENDIX

Acute Appendicitis with Acute Local Peritonitis—Table 2 summarizes the largest single group, namely, acute appendicitis with acute

TABLE 2—*Analysis of Acute Appendicitis with Acute Local Peritonitis—Thirty-One Cases*

	Number	Per Cent		Number	Per Cent
Time			White blood cells 16,000 +	21	75*
12 hours	7	23*	White blood cells 16,000 —	7	25*
24 hours	15	48*	Polymorphonuclears 80% +	21	78*
48 hours	6	19*	Polymorphonuclears 80% —	6	22*
72 hours	1	3	Mild	21	68*
96 hours	0	0	Moderate	10	32*
96+ hours	2	6	Severe	0	0*
Nausea +	24	77	1 to 20 years	15	48
Nausea 0	7	23	21 to 40 years	10	32
Vomiting +	20	67	40+ years	6	19
Vomiting 0	10	33	Fluid		
Chill +	2	14	Little	20	94*
Chill 0	12	86	Much	2	6*
Fever +	26	87	Clear	6	19*
Fever 0	4	13	Turbid	25	81*
Typical	24	77*	Thick	0	0
Atypical	7	23*	Smear (forms seen)		
Diarrhea +	2	8	?	11	
Diarrhea 0	23	92	0	17	83*
Constipation +	7	28	1	3	15*
Constipation 0	18	72	2	0	0
Obstipation +	0	0	3	0	0
Obstipation 0	24	100	Bacterial Growth		
Quadrant 1	21	68*	0 species	24	77*
Quadrant 2	7	23*	1 species	3	10*
Quadrant 3	1	3	2 species	0	0*
Quadrant 4	2	6	3 species	3	10*
Tenderness +	31	100	4 species	1	3*
Tenderness 0	0	0	5 species	0	0
Rigidity +	18	62	6 species	0	0
Rigidity 0	11	38	B. coli	5	16*
Rebound tenderness +	15	80	Green streptococcus	2	6*
Rebound tenderness 0	5	20	C. welchii	2	6*
Distention +	0	0	Sequelae 0	22	71*
Distention 0	14	100	1 to 3	9	29*
Mass +	0	0	4 to 7	0	0*
Mass 0	25	100	Days 15 —	25	81*
Pelvic signs +	19	63	Days 16 +	6	19*
Pelvic signs 0	11	37	Recovered	31	100*
			Died	0	0*

* As stated in the paper, only the striking features are significant, in this and the following tables, those points which seem to us of importance are indicated by an asterisk.

local peritonitis, comprising thirty-one cases. It seems to us that the significant points in this group are: More than two thirds of the patients came to the hospital within the first twenty-four hours and almost all of them within two days. About four-fifths had a typical history, which probably rendered an early diagnosis easy. In two thirds of the cases the signs were limited to one quadrant of the abdomen. Three fourths of the cases showed a total white cell count above 16,000 and polymorphonuclears over 80 per cent, which was the average count for the whole series. These cases averaged 18,000 white blood cells

with 85 per cent polymorphonuclears. None of the patients seemed to be seriously ill, two-thirds were considered to be mild cases, and only one-third were moderately ill. Two thirds of the patients had no untoward postoperative symptoms, and the other third had relatively few and mild ones. All of the patients recovered, and five sixths of them left the hospital within fifteen days. With regard to the peritoneal fluid, the quantity was relatively small in four fifths of the cases. It was turbid in most, and not thick in any case. It was without odor in all instances. In one third of these cases no smear was made of the peritoneal fluid, of the other two-thirds, 85 per cent showed no organisms and 15 per cent (three cases) showed only a single type. Of these three, one proved to grow a single organism but the other two grew three and four species, respectively. No gram-positive bacilli were seen in the smear, although seven species of these types grew out, which indicates that they were present in relatively few numbers in the peritoneal fluid. The cultures yielded no growth in twenty-four, or 77 per cent, of the cases. Cultures were positive in seven cases, or 23 per cent. The most common species was nonhemolytic *B. coli*, which appeared in five cases, while the green streptococcus, *C. welchii* and aerobic and anaerobic diphtheroids appeared in two cases each. Three of the seven cases yielded a single species on culture. Two of these were *B. coli* and one an anaerobic diphtheroid. In three cases three species were found and in one, four. In the latter case, only one form was seen in the smear, so that the others must have been present in extremely small numbers.

Acute Appendicitis with Acute Diffuse Peritonitis—There were only four cases in this group, so that any conclusions drawn from them may be misleading. The points wherein they differ from the larger group are, however, suggestive. All of the patients had nausea, vomiting and fever. All had signs in more than one quadrant of the abdomen. All had tenderness and rigidity, while rebound tenderness was noted in three but not mentioned in one. All had a differential polymorphonuclear count of over 85 per cent, although the total count fell below 16 000 in one case. All the patients were more than mildly ill. All recovered, but three had to stay in the hospital more than sixteen days. Bacterial growth was found in the peritoneal exudate in all but one case, but *C. welchii* was not found.

Acute Appendicitis with Localized Abscess—There were only two cases of acute appendicitis without gangrene or perforation in which a localized abscess had developed. These cases differ from those in the preceding two groups in that in both the symptoms were of more than four days' duration. Both had signs limited to one quadrant. *B. coli* was found in both cases and the patients required hospitalization for

more than sixteen days. The cases are similar to those in the preceding group in that in both there were nausea, vomiting and fever; the patients were more than mildly sick, and neither group yielded *C. welchii*.

Comment on the Cases of Acute Appendicitis Without Gangrene or Perforation—The recovery of all of the patients with acute appendicitis accompanied with acute local peritonitis is the most striking feature of table 2. These patients came to the hospital early before the appendix had ruptured or the contained organisms had entered and multiplied in the peritoneal cavity. One would expect to find that these two facts were in some way related to one another. Localization of signs corresponded to localization of infection. Symptoms and signs were of importance only as they pointed to the diagnosis. A high white cell count was usually found. The general aspect of the patients indicated a relatively benign disease. The peritoneal reaction was limited in extent. There was usually not much fluid, but it was turbid, indicating cellular elements. Smears and cultures were generally negative. The turbidity of the fluid does not indicate the presence of bacteria, necessarily. Seven of these cases demonstrate that it is possible for bacteria to penetrate a grossly intact wall of the appendix. *B. coli* apparently is most likely to do this, *C. welchii* and green streptococci may do it. Stout²⁹ demonstrated that the mucosa is broken in all cases of acute appendicitis. Organisms presumably invade the wall and may move about in the circulating fluid or be carried about by phagocytes. Leukocytes are given off into the peritoneal cavity and may carry with them viable organisms. If they are not destroyed by the phagocyte, they may in turn multiply within it and destroy it and thus be liberated in the peritoneal cavity. *C. welchii* frequently repels leukocytes, and it may be less frequently carried by them through the wall of the intestine. In the four cases of acute appendicitis with acute diffuse peritonitis the process had gone a little farther than in the preceding group, but there had been no localization. Signs were present indicative of wider spread of infection but still the organisms were not present in very great numbers. The sequelae indicated that the body had more trouble overcoming the infection than it did in the preceding group of cases. In the cases of abscess, the organisms or their products had been carried through the wall or had penetrated to such a degree that a strong exudative reaction had been set up by the peritoneum. There was sufficient time, however, for this defense to establish itself and control the spread of the infection by a plastic process. The organisms were able to gain a foothold and multiply outside of the wall of the appendix. Just what part the resistance of the individual

29 Stout, A. P. Unpublished work.

and the virulence of the organisms had to play in this and how much it was due to pure chance of anatomic location, it is difficult to say

Perforated Appendix with Acute Local Peritonitis—In contradistinction to the group of cases of acute appendicitis in which there was no gangrene and no perforation, the perforated appendixes usually

TABLE 3—*Analysis of Perforated Appendix with Acute Diffuse Peritonitis—Eleven Cases, Perforated Appendix with Abscess—Twelve Cases*

	Acute Diffuse Peritonitis	Per Cent	Appendix with Abscess	Per Cent		Acute Diffuse Peritonitis	Per Cent	Appendix with Abscess	Per Cent
Time					White blood cells				
12 hours	0	0	1	8	16,000 +	3	30*	7	64*
24 hours	1	9	0	0	16,000 —	7	70*	4	36*
48 hours	4	36*	1	8	Polymorphonuclears				
72 hours	2	18*	2	17*	80% +	5	50*	7	70*
96 hours	2	18*	3	25*	80% —	5	50	3	30*
96+ hours	2	18*	5	42*	Mild	0	0	1	8
Nausea +	9	90	11	92	Moderate	6	55*	8	67*
Nausea 0	1	10	1	8	Severe	5	45*	3	25*
Vomiting +	9	82	11	92	1 to 20 years	6	55	3	25
Vomiting 0	2	18	1	8	21 to 40 years	1	9	2	17
Chill +	3	50	2	33	40+ years	4	36	7	58
Chill 0	3	50	4	66	Fluid				
Fever +	11	100	12	100	Little	2	18	2	17
Fever 0	0	0	0	0	Much	9	82*	10	83*
Typical	8	73*	9	75*	Clear	0	0	0	0
Atypical	3	27*	3	25*	Turbid	8	73*	3	25
Diarrhea +	2	29	0	0	Thick	3	27	9	75*
Diarrhea 0	5	71	10	100	Smear (forms)				
Constipation +	4	57	4	33	?	0	0	1	
Constipation 0	3	43	8	67	0	0	0	1	9
Obstipation +	1	14	0	0	1	0	0	0	0
Obstipation 0	6	86	11	100	2	7	64*	3	27*
Quadrant 1	2	18	6	50	3	4	36*	7	64*
Quadrant 2	0	0	4	33	Bacteria (growth)				
Quadrant 3	1	9	0	0	0 species	0	0*	0	0
Quadrant 4	8	73	2	17	1 species	1	9*	0	0
Tenderness +	11	100	12	100	2 species	2	18*	2	17*
Tenderness 0	0	0	0	0	3 species	3	27*	4	33*
Rigidity +	10	91	10	91	4 species	4	36*	2	17*
Rigidity 0	1	9	1	9	5 species	1	9*	2	17*
Rebound tenderness +	7	88	3	75	6 species	0	0*	2	17*
Rebound tenderness 0	1	13	1	25	B coli	11	100*	12	100*
Distention +	4	80	5	63	Green streptococcus	6	55*	9	75*
Distention 0	1	20	3	38	C welchii	3	27*	7	58*
Mass +	1	17	7	70	Sequelae 0	2	18	4	36
Mass 0	5	83	3	30	1 to 3	4	36*	6	55*
Pelvic +	6	60	3	30	4 to 7	5	46*	1	9
Pelvic 0	4	40	7	70	Days 15—	2	18	2	17
					Days 16+	9	82*	10	83*
					Recovered	8	73*	10	83*
					Died	3	27*	2	17*

resulted in either a well walled-off abscess or an extensive diffuse process. Acute local peritonitis was found in only two cases of this series. These do not differ strikingly from the other two groups of perforated appendixes. It has been impossible in most of the cases of this group to determine from the history just when the perforation took place. It may be that in these two instances it had occurred a relatively short time before operation. One point seems to be of significance in these two cases. Both patients recovered, although both yielded four different species of organisms from the peritoneal exudate, includ-

ing *B coli*. However, one was in the hospital sixty-one days after operation and had numerous complications. The other had no sequelae and went home on the twenty-first day. The culture from the former yielded *C welchii* and the hemolytic streptococcus as well as *B coli*, in the latter case, these other organisms were absent.

Perforated Appendix with Acute Diffuse Peritonitis—This group contains eleven cases and may be contrasted with the one that follows in which perforation was present with abscess. Table 3 brings out several striking dissimilarities between these two groups, and both of them in turn differ in many respects from the first group which is shown in table 2. It is seen that the majority of the patients came to the hospital after forty-eight hours of symptoms, and only one came in the first twenty-four hours. Still, three fourths of these cases gave a typical history, and the disease should have been diagnosed almost as easily as in the first group. Nausea, vomiting, chill, fever, diarrhea, constipation and obstipation were all more prominent features of the history. Three fourths of the patients gave signs in all four quadrants of the abdomen, while tenderness, rigidity, rebound tenderness and distention were more frequent. On the other hand, the blood counts were much lower as a rule, the total count being below 16,000 in 70 per cent and the polymorphonuclear percentage below 80 per cent in half of the cases. None of the cases was mild, and in half of them the patients were markedly ill at the time of operation. Only two were in the hospital for less than fifteen days, and both of them died. The average period of hospitalization for those who did not die was thirty days. All but two of the patients had postoperative complications. Marked infection of the abdominal wall was the most frequent untoward sequel. Four of the patients had pneumonia. Three of the patients died. The peritoneal exudate was in great quantity in all but two of the cases. No odor was present in four of the cases, while in four others it was foul and in two fecal. No observation with regard to this point was made in one case. All of the smears from the fluid showed at least two forms of bacteria, and four of them showed all three. No cultures were sterile, and seven of the eleven yielded from three to four different species. In every case nonhemolytic *B coli* was found, and in four the hemolytic variety as well. More than half showed the green streptococcus and one fourth *C welchii*, while one third of the cases yielded an anaerobic streptococcus. The three fatal cases had these things in common: the patients were over 45 years of age, more than five complications occurred, and a thick fluid was present with a combination of nonhemolytic *B coli* and the green streptococcus. Only one of the fatal cases yielded *C welchii*.

Perforated Appendix with Abscess—The twelve cases in this group are summarized with the preceding group in table 3. They differ from

those in the former group in having a longer history of symptoms, two thirds of them having lasted for more than four days. Nausea, vomiting and fever were prominent features, but diarrhea, constipation or obstipation were not. As in the preceding group, the history was typical in three fourths of the cases. The signs were generally limited to one or two quadrants. As with the cases of diffuse peritonitis, most of the patients with abscess were moderately or markedly ill. The blood counts in general were higher, but the "resistance line" of Gibson³⁰ indicated an unfavorable prognosis in two thirds of the cases. Two of the patients died, both showing a falling "resistance line." In those who survived, the complications were mild, while in the diffuse cases they were severe. The survivors, as in the preceding group, stayed in the hospital on an average of about a month. The peritoneal exudate was present in considerable quantities and was usually thick. It had a foul odor in three fourths of the cases. In ten of eleven, more than one morphologic form was seen in the smear and in seven, three kinds were present. As in the preceding group, gram-positive bacilli were never seen in the absence of both gram-negative bacilli and gram-positive cocci. All yielded nonhemolytic *B. coli*, the green streptococcus was present in three fourths of the cases and *C. welchii* in half. Again, half of the cases yielded four or more different species, six being found in two cases and five in two. The two fatal cases had in common much fluid with a foul odor yielding *B. coli* and green streptococci. Only one had *C. welchii*. Both were 65 years of age or over.

Localized Abscess in the Right Lower Quadrant with Questionable Perforation of the Appendix—There were five cases with large abscesses in the right lower quadrant in which the appendix could not be seen and no effort was made to remove it. They were similar in many ways to the preceding group, and might have been classified with them. The exudate in four of these five cases was present in large amount and was thick. The smears showed two or more forms, and the cultures two or more species. Nonhemolytic *B. coli* was present in all of these cases, green streptococcus in two and *C. welchii* in only one which was not fatal.

Comment on Cases of Perforated Appendix—The majority of the patients in these groups came to the hospital late in spite of the fact that in three fourths of the cases there was a typical history of pain. The question is not yet settled as to the cause of perforation of an appendix. Except for the rare penetration of a foreign body, we must presuppose a death of tissue and a solution of continuity of tissue fibers.

30 Gibson C. L. The Value of the Differential Leucocyte Count in Acute Surgical Diseases. *Ann Surg* 43:485, 1906.

either by liquefaction or by rupture from pressure. Clinically, it has been thought possible at times to tell when perforation has taken place either by a sudden relief from pain, due supposedly to the release of distention of the inflamed appendix, or a sudden increase of pain from the irritation of a large area of peritoneal serosa by a quantity of intestinal contents. In both of these instances, there is probably an explosive element to the perforation. In most cases, however, it is not possible to tell when the perforation has taken place, and in these instances the element of force in the rupture is probably minimal. In either case, as the wall breaks or parts, the contents, including bacteria, disintegrating food particles and digestive ferments, escape. The amount depends on the size of the opening and the force behind it. It is of interest that in our group of twenty-five cases of known perforation of the appendix, two were found in an early stage of acute local peritonitis, and the patients recovered. The eleven patients with acute diffuse peritonitis came in late, in spite of the fact that three fourths of them had a typical history. Symptoms and signs were all extensive. The patients were markedly ill, the infection had spread extensively, as indicated by the large quantity of fluid which showed bacteria on smears and yielded positive cultures in every case. In these there was no evidence of the body's ability to localize the infection. The blood count suggests a losing battle against overwhelming odds. It is possible that some of these patients would eventually have overcome the infection without operation, but it is fair to assume that operation with the removal of the distributing focus, thus stopping the outpouring of fecal material, stemmed the tide of spread and gave the body a chance to overcome the infection if it could. This it failed to do in one fourth of the cases. In the twelve cases of abscess we must presuppose either that there was a wall already prepared before the perforation or that the spread of infection was so slow that time was given for the protective mechanism to be built up. In several of these cases, although there was definite abscess formation, there was some degree of diffuse inflammation around the abscess. In a number of cases, when the peritoneal cavity was opened, an excess of peritoneal fluid was found, and later an abscess was located containing exudate of a different character. Smears and cultures of these free fluids usually revealed either no organisms or fewer organisms than the abscess fluid, showing that the general peritoneum was either reacting to diffusible products of the local infection or destroying the organisms that were wandering afield or else that certain organisms were able to spread abroad against the defense of the peritoneal fluid while others could not. It would seem to be worthy of note that *C. welchii* was found in the peritoneal fluid in only twelve of the thirty cases of perforative appendicitis and in only two of the six fatal cases. This organism is so easily identified

that we feel confident that this figure represents the actual incidence of *C welchii* in our specimens. Our results seem to indicate either that it is not so frequent as is supposed to be in the ileocecal region, or that it could not maintain itself in the peritoneal cavity. Perhaps the latter condition is not surprising when we know that it grows best on glyco-genic tissues. In this group of cases it does not seem to have been a very potent factor in the mortality, and it may be that in association with other organisms it cannot produce its potent toxin. It is true that certain organisms will prevent the formation of toxin when growing with *C welchii* in vitro. It would seem to be fair to assume that if a perforation of the intestine takes place, a larger mass of organisms enters the peritoneal cavity through this gross aperture than would ordinarily come through an intact wall. In the cases with perforation therefore, we have to deal with a relatively large initial bacterial dosage which cannot be measured, and a certain amount of intestinal juice containing more or less active digestive ferments and also foreign bodies in the form of partially digested or indigestible food. What part the latter substances play in the development of peritonitis it is difficult to say, but from what we know of the irritating character of these substances, they may be of considerable importance. This is a question warranting further investigation.

Gangrenous Appendicitis Without Perforation with Acute Local Peritonitis—There were six cases in which the appendix was gangrenous either as a whole or in part without any gross evidence of perforation, but was surrounded by a local uncircumscribed area of peritonitis (table 4). All but one of these patients came to the hospital within forty-eight hours of the onset of symptoms. All but one gave a typical history. All were either mildly or moderately ill. In four, the signs were limited to one quadrant. The sequelae were mild, and all the patients recovered. The peritoneal fluid was turbid in all cases but without odor. The smear showed no organisms in two, but was positive in three. Only one showed no growth, four of the others showed two or more bacteria. The nonhemolytic *B coli* was present in only one-half of the cases, the green streptococcus was present in only one case. *C welchii* was not found at all.

Gangrenous Appendicitis Without Perforation with Acute Diffuse Peritonitis—There were only two cases in this group. They differed from those in the preceding group in the greater severity of symptoms and the greater extent of the signs but recovery resulted in both with only mild sequelae. There was much peritoneal exudate, but it had no odor. In one fluid no organisms were seen on smear, but four different species grew out of both fluids. Nonhemolytic *B coli* was present in both cases but the green streptococcus in only one and *C welchii* in neither.

Gangrenous Appendicitis Without Perforation with Localized Abscess—Only one case in the series fell into this group. A definitely localized abscess was found in this case. The lesion differed from that in the cases in the preceding group chiefly in its localization. The patient recovered with mild sequelae. The smear showed gram-positive cocci as well as gram-negative bacilli, but only the latter appeared in the culture.

TABLE 4—*Analysis of Gangrenous Appendix Without Perforation with Acute Peritonitis—Six Cases, with Acute Diffuse Peritonitis—Two Cases*

	Acute Local Peritonitis	Per Cent	Acute Diffuse Peritonitis	Per Cent		Acute Local Peritonitis	Per Cent	Acute Diffuse Peritonitis	Per Cent
Time					White blood cells				
12 hours	1	17*	0	0	16,000 +	4	67	1	50
24 hours	2	33*	1	50	16,000 —	2	33	1	50
48 hours	2	33*	1	50	Polymorphonuclears				
72 hours	1	17*	0	0	80% +	5	83	1	50
96 hours	0	0	0	0	80% —	1	17	1	50
96+ hours	0	0	0	0	Mild	2	33+	0	0*
Nausea +	5	83	2	100	Moderate	4	67*	2	100*
Nausea 0	1	17	0	0	Severe	0	0	0	0
Vomiting +	3	50	2	100	1 to 20 years	0	0	0	0
Vomiting 0	3	50	0	0	21 to 40 years	4	67	2	100
Chill +	1	17	0	0	40+ years	2	33	0	0
Chill 0	2	67	0	0	Fluid				
Fever +	5	83	2	100	Little	4	67	0	0
Fever 0	1	17	0	0	Much	2	33	2	100
Typical	5	83	1	50	Clear	0	0	0	0
Atypical	1	17	1	50	Turbid	6	100	2	100
Diarrhea +	0	0	0	0	Thick	0	0	0	0
Diarrhea 0	4	100	2	100	Smear (forms)				
Constipation +	2	33	1	50	?	1		0	
Constipation 0	0	33	1	50	0	2		1	50
Obstipation +	0	0	0	0	1	1	40	0	0
Obstipation 0	4	100	2	100	2	2	40+	0	0
Quadrant 1	4	67	0	0	3	0	0	1	50
Quadrant 2	1	17	1	50	Bacteria (growth)				
Quadrant 3	1	17	0	0	0 species	1	17+	0	0
Quadrant 4	0	0	1	50	1 species	1	17+	0	0
Tenderness +	6	100	2	100	2 species	3	50+	0	0
Tenderness 0	0	0	0	0	3 species	0	0	0	0
Rigidity +	5	83	2	100	4 species	0	0	2	100*
Rigidity 0	1	17	0	0	5 species	1	17+	0	0
Rebound tenderness +	5	100	2	100	6 species	0	0	0	0
Rebound tenderness 0	0	0	0	0	B coli	3	50+	2	100+
Distention +	1	17	2	100	Green streptococcus	1	17+	1	50*
Distention 0	5	83	0	0	C welchii	0	0+	0	0*
Mass +	0	0	0	0	Sequelae 0	2	33+	1	50*
Mass 0	5	100	2	100	1 to 3 days	4	67+	1	50*
Pelvic sign +	3	60	1	50	4 to 7 days	0	0	0	0
Pelvic sign 0	2	40	1	50	Days 15—	2	33+	0	0
					Days 16+	4	67+	2	100*
					Recovered	6	100*	2	100*
					Died	0	0	0	0

Comment on Gangrenous Appendix Without Perforation—Our observations in these nine cases are surprising in two respects. First, the great majority of them resulted merely in a local peritonitis, one as an abscess and the other six as simple acute local peritonitis. It is quite possible that perforation would have occurred in all of these cases, but operation was performed in the preperforative stage before organisms had invaded the peritoneal cavity in very great numbers. Secondly, although other intestinal organisms were found in culture, *C. welchii*

was not recovered from a single case in the group. This would lead us to believe that, contrary to the opinion of Weinberg and others, this organism is usually not particularly active in the gangrene of appendicitis, and this is further confirmation of our observations in the cases with perforation. One may ask, "What about the other anaerobes?" If we include our cases of perforative appendicitis with our gangrenous group, as we think we may fairly do, we find that in our series there were thirty-nine definitely gangrenous lesions of the appendix and thirty-seven definitely nongangrenous lesions. Twenty-eight different species were found in the nongangrenous cases and one hundred and twenty-four in the gangrenous cases, but if we study the proportion of aerobes to anaerobes in these two groups, we find that in the nongangrenous cases the aerobes represented 75 per cent and the anaerobes 25 per cent, while in the gangrenous cases the aerobes comprised 72 per cent and the anaerobes 28 per cent. We can only say, for our series at least, that in the gangrenous cases we were not able to cultivate anaerobes from the peritoneal fluid in any greater proportion relative to the aerobes than in the nongangrenous cases. Whether they were more numerous within the lumen of the appendix as Weinberg has stated, we are not able to judge. Perforative lesions were found in almost all of Heyde and Runeberg's cases, and these showed many gram-negative anaerobes. The cause of gangrene of the appendix or the intestine has been the subject of much speculation and discussion in the literature on peritonitis. In general, two factors have been considered, the interference of blood supply and the direct action of bacteria. We know that in other parts of the body the simple cutting off of the blood supply results in local death, as for example, in popliteal aneurysm or arteriosclerotic gangrene of the foot. In the intestine or appendix it is impossible to have a sterile gangrene, but the cutting off of the blood supply by strangulation or by edema or by local thrombosis almost certainly plays a part. We do not agree with Corner,³¹ who makes the element of time the criterion of whether or not the gangrene of strangulated hernia is due to bacterial action or due to the cutting off of the blood supply. He believed that gangrene developing within twenty-four hours was due primarily to bacterial action. It is obvious that there are usually different mechanical factors operating to make the cutting off of blood supply of an appendix different from that of the intestine. In the former, the small size of the lumen increases the element of pressure from within when edema of the wall or impaction of fecaliths takes place. In the latter, except in the cases of mesenteric thrombosis or an impacted gallstone, the pressure on blood vessels is usually exerted from without. Kelly¹⁸

31 Corner E M. Acute Infective Gangrenous Processes (Necroses) of the Alimentary Tract. Erasmus Wilson Lecture, Lancet 1 1410 1904

presented as a rarity a case in which there seemed to be gangrene of the mucous membrane of an appendix without edema of the rest of the wall, and this he thought to be due to bacterial action rather than to occlusion of a blood vessel. We know of certain conditions, such as hemolytic streptococcus gangrene³² or gangrene of the abdominal wall,³³ due apparently to the symbiosis of intestinal organisms, in which bacterial activity seemed to be the primary factor, but even with these it is not clear whether it is the result of the direct action of bacterial products on the tissues or the secondary result of thrombosis of blood vessels or their occlusion by edema. Are there bacteria within the intestine that can of themselves or in combination with other organisms, aerobic or anaerobic, so injure mucous membrane that they may invade the tissues, or must the primary insult be due to a mechanical injury? Heyde²² and others expressed the belief that while some bacteria may be able to act directly, others that enter the tissues at a point of injury adapt themselves to the body fluids, increase in virulence, become pathogenic, and then proceed to act directly on the tissue. While we do not question the possibility of this, particularly when more than one species is present, we believe that in the case of the appendix the factor of the occlusion of the blood vessel is of prime importance before liquefaction and perforation can take place. We have frequently seen thrombosed vessels near local areas of gangrene or thrombosis of mesenteric vessels when extensive gangrene of the appendix has taken place. Of particular interest and importance is the fact that in many gangrenous appendixes the gangrene extends down to within 1 cm of the cecum and then stops, fortunately for the surgeon, leaving enough relatively normal wall for inverting the stump. This portion of the appendix is not easily occluded, and it may derive its blood supply from the cecal wall or from the artery that comes up through the wall and makes its exit into the mesentery about 1 cm from the cecum. This would seem to lend weight to the idea that gangrene of the intestine does not usually take place by the action of bacteria where it is difficult to interfere with the blood supply of the part.

LESIONS OF THE SMALL INTESTINE

Ten of the cases fall under this heading. They are analyzed in table 5. For purposes of comparison, they may be divided into two groups, those in which the lesions were perforative and those in which

32 Melenev, F. L. Hemolytic Streptococcus Gangrene, *Arch. Surg.* 9:317 (Sept.) 1924.

33 Brewer, G. E. and Melenev, F. L. Progressive Gangrenous Infection of the Skin and Subcutaneous Tissues, Following Operation for Acute Perforative Appendicitis. A Study in Symbiosis, *Ann. Surg.* 84:438 1926.

they were obstructive. The latter group consists of two cases of strangulated hernia and two cases of volvulus.

Perforative Lesions of the Small Intestine—Fever was a prominent feature. Constipation, obstipation and distention were of no particular importance. The total blood count was low, and the number of polymorphonuclears proportionally high. On the patient's admission to

TABLE 5.—*Analysis of Lesions of the Small Intestine, Perforative—Six Cases*
Nonperforative—Four Cases

	Perforative	Per Cent	Nonperforative	Per Cent		Perforative	Per Cent	Nonperforative	Per Cent
Time					Polymorphonuclears				
12 hours	3	50*	0	0	80% +	3	60*	2	100*
24 hours	2	33*	2	50*	80% —	2	40*	0	0
48 hours	0	0	1	25*	Mild	0	0	0	0
72 hours	0	0	0	0*	Moderate	4	67*	2	50*
96 hours	0	0	1	25*	Severe	2	33*	3	50*
96+ hours	1	17	0	0	1 to 20 years	0	0	0	0
Nausea +	4	80	4	100	21 to 40 years	2	33*	2	50*
Nausea 0	1	20	0	0	40+ years	4	67*	2	50*
Vomiting —	4	80	4	100	Fluid				
Vomiting 0	1	20	0	0	Little	2	33	2	50
Chill +	0	0	0	0	Much	4	67*	2	50
Chill 0	3	100	1	100	Clear	0	0	0	0
Fever —	5	83	2	50	Turbid	5	83*	3	75*
Fever 0	1	17	2	50	Thick	1	17*	1	25*
Diarrhea —	0	0	1	33	Smear (forms)				
Diarrhea 0	6	100	2	67	?	1		1	
Constipation +	2	33	4	100	0	3	60*	2	67*
Constipation 0	4	67	0	0	1	0	0*	0	0*
Obstipation +	0	0	3	100*	2	1	20*	0	0*
Obstipation 0	6	100*	0	0	3	1	20*	1	33*
Quadrant 1	1	17*	2	50*	Bacteria (growth)				
Quadrant 2	1	17*	0	0*	0 species	1	17*	0	0
Quadrant 3	1	17*	0	0*	1 species	0	0*	1	25*
Quadrant 4	3	50*	2	50*	2 species	1	17*	1	25*
Tenderness —	5	100	4	100	3 species	1	17*	0	0*
Tenderness 0	0	0	0	0	4 species	1	17*	2	50*
Rigidity —	6	100	0	0	5 species	1	17*	0	0
Rigidity 0	0	0	2	100	6 species	1	17*	0	0
Rebound tenderness +	1	100	0	0	B. coli	3	50*	4	100*
Rebound tenderness 0	0	0	2	100	Green streptococcus	4	67*	0	0*
Distention —	1	17*	4	100*	C. welchii	3	50*	2	50*
Distention 0	5	83*	0	0*	Sequellae 0	1	20	0	0
Mass —	0	0	2	67	1 to 3	2	40*	3	75*
Mass 0	5	100	1	33	4 to 7	2	40*	1	25
Pelvic signs —	2	40	0	0	Days 15—	3	50	0	0
Pelvic signs 0	3	60*	1	100*	Days 16+	2	50	4	100
White blood cells					Recovered	2	33	3	75*
16,000 +	1	20*	1	50*	Died	4	67*	1	25
16,000 —	4	80*	1	50*					

the hospital the severity of the condition in the cases with perforation seemed to be about the same as in the cases with obstruction, but the complications were more severe, and four of the six cases were fatal. In three cases, the peritoneal exudate showed nothing in the smear. In one of these in which a lesion of the upper part of the jejunum had become sealed off, no growth was found. In another the fluid specimen came from a patient with a perforated duodenal ulcer. A nonhemolytic and also a green streptococcus were cultivated. The exudate from another case of perforated duodenum showed nothing on smear but

yielded four different species on culture. This case and the other three in which the ileum had perforated, with from three to five different species of bacteria cultivated from the peritoneal fluid were fatal. The other two patients recovered.

Nonperforative Lesions of the Small Intestine—This group of four cases includes two cases of strangulated hernia with gangrene of the intestine that required resection and two cases of postoperative volvulus. These cases differed from those in the preceding group in that fever was not a prominent symptom while constipation, obstipation and distention were marked. The severity of the cases before operation was judged to be as great as in the cases with perforation, and yet only one of the patients died and the others recovered without serious complication. The fatal case was one in which the volvulus was not relieved at operation, and we feel that this rather than the peritonitis was the chief factor in the fatal outcome. In the two cases of strangulated hernia the intestine was gangrenous without gross perforation. From each of these, four species of bacteria were recovered. *B. coli* and *C. welchii* were present in both, but the green streptococcus was absent. Both patients recovered.

Comment on the Lesions of the Small Intestine—The most striking feature in this group is that in the cases with and without perforation the patients' condition seemed to be about equally severe on admission to the hospital, but that after operation four of the six patients with perforative lesions died and only one with obstruction succumbed. In the former group, there was distention in only one case while in the latter group it occurred in all of them. It is obvious that the cause of the clinical severity in these two groups is different. In the group with perforation it is probably due primarily to the bacterial or chemical action within the peritoneal cavity. In the latter it is manifestly due to the obstruction of the intestine. Relief could not be obtained in the former so that the three patients with ileal perforations and the one with duodenal perforation of long standing died, in the other cases obstruction could be and was relieved, except in one case in which the cause of the obstruction was not found and a simple short circuiting operation was not sufficient. The patient in this case died on account of the obstruction rather than on account of the peritonitis as autopsy showed even though hemolytic streptococci and *B. coli* were recovered from the peritoneal exudate. In the group of cases with perforation the only two patients to recover were those with duodenal and jejunal perforations in whom bacterial contamination of the peritoneal cavity was minimal. When the perforation was closed there was no further increase of the irritating factor. The bacterial cultures in this series were interesting. *B. coli* was found in all three and *C. welchii* in two of the cases of obstruction in which

the patients survived. We may assume that because there was no perforation, the bacterial dosage was small and there was no intestinal fluid except that which may have seeped through the wall. *B. coli*, *C. welchii* and the green streptococcus were all present in three of the four fatal cases with perforation. Because of the perforation we may assume that the dosage of bacteria was greater than in the group without perforation, but we cannot overlook the fact that the intestinal

TABLE 6—*Analysis of the Lesions of the Large Intestines, Perforative—Five Cases, Nonperforative—One Case*

	Number	Per Cent		Number	Per Cent
Time			Poly morphonuclears		
12 hours	1	17*	80% +	3	60*
24 hours	2	33*	80% —	2	40*
48 hours	1	17*	Mild	0	0
72 hours	0	0*	Moderate	3	50*
96 hours	1	17*	Severe	3	50*
96+ hours	1	17*	1 to 20 years	0	0
Nausea +	4	67	21 to 40 years	1	17
Nausea 0	2	33	40+ years	5	83*
Vomiting +	4	67	Fluid		
Vomiting 0	2	33	Little	1	17
Chill +	5	83	Much	5	83*
Chill 0	1	17	Clear	0	0
Fever +	5	100	Turbid	5	83
Fever 0	0	0	Thick	1	17
Diarrhea +	2	33	Smear (forms seen)		
Diarrhea 0	4	67	?	1	
Constipation +	5	83	0	1	20
Constipation 0	1	17	1	1	20
Obstipation +	3	50	2	2	40
Obstipation 0	3	50	3	1	20
Quadrant 1	0	0	Bacterial growth		
Quadrant 2	1	17*	0 species	1	17
Quadrant 3	1	17*	1 species	0	0
Quadrant 4	4	67*	2 species	0	0
Tenderness +	6	100	3 species	1	17*
Tenderness 0	0	0	4 species	2	33*
Rigidity +	6	100	5 species	2	33*
Rigidity 0	0	0	6 species	0	0
Rebound tenderness +	2	33	<i>B. coli</i>	5	83*
Rebound tenderness 0	1	17	Green streptococcus	3	50*
Distention +	5	100	<i>C. welchii</i>	5	83*
Distention 0	0	0	Sequelata ?	1	
Mass +	1	20	0	1	20
Mass 0	4	67	1 to 3	2	40
Pelvic signs +	3	50	4 to 7	2	40
Pelvic signs 0	3	50	Days 15--	1	17
White blood cells 16,000 +	3	50*	Days 16+	5	83*
White blood cells 16,000—	3	50*	Recovered	5	83*
			Died	1	17

juices and food particles were also present to a variable degree. It is difficult to say whether the fatal outcome in these cases was due to the bacterial dosage or to the added effect of the intestinal contents.

LESIONS OF THE LARGE INTESTINE

Perforative Lesions of the Large Intestine—There were five of these cases in the series, four of them with acute diffuse, and one with acute local, peritonitis (table 6). Three of the five patients came to the hospital within twenty-four hours. Constipation was a frequent symptom, with obstipation in two cases. Four of the five patients had signs in all four quadrants and in all, the abdomen was

distended. None had mild cases, the majority were severely ill. In one case there were no sequelae, in three, the complications were severe. One patient died soon after operation before there was time for complications, the rest recovered. There was considerable turbid fluid in all but one case, in three, the odor was fecal, but in two the fluid was described as having no odor. The four smears which were examined showed organisms, and all of the cultures yielded three or more different species. Nonhemolytic *B. coli* and hemolytic *C. welchii* were present in every case, while the green streptococcus appeared in three.

Nonperforative Lesion of the Large Intestine—There was only one case in this series, and it is of interest only so far as it differs from the cases in the group with perforation. It was a case of volvulus of the sigmoid of moderate severity, with three quadrants involved. There was much turbid fluid without odor. No organisms were seen in the smear, and the culture yielded no growth. The patient recovered with only one mild sequel.

Comment on Lesions of the Large Intestine—The cases of perforative lesion of the large intestine are perhaps surprising in two respects, one being that only one of the five patients died, although all of the patients were quite ill on admission. The patient who died came to the hospital almost moribund and died directly after operation. Nevertheless, *C. welchii* were found in all five patients, and all were over 40 years of age. This mortality figure differs strikingly from that in the group of cases of perforative lesions of the small intestine. Tavel and Lanz¹⁰ made the same observation and offered as an explanation the facts that the contents of the small intestine are more fluid and more likely to be spread around after discharge into the peritoneal cavity, because of both the consistency and the greater movement of the intestines. On the other hand, the contents of the large intestine are more solid and the intestine is less freely movable, so that there is less extensive spread. These seem to be logical explanations, but we should like to emphasize two other factors: the irritating effect of the digestive fluids of the small intestine and the greater viability of the bacteria in the small intestine. The absence of lethal activity on the part of *C. welchii* is consistent with our foregoing observations with respect to the perforative and gangrenous appendixes and the lesions of the small intestine.

LESIONS OF THE GALLBLADDER

Acute Cholecystitis with Peritonitis—There were six cases in this series (table 7). In three the gallbladder had perforated, in two, there was acute diffuse peritonitis and in the other a well localized abscess had formed. In two of the three cases without perforation

acute local peritonitis occurred and acute diffuse peritonitis with acute pancreatitis in one. Most of the patients came to the hospital early because of the severity of their symptoms. All had nausea, vomiting and fever without chills. In the cases with perforation three or four quadrants were involved, while in the others the signs were limited to one or two quadrants. Distention was a prominent feature. Only one

TABLE 7—*Analysis of Acute Cholecystitis—Six Cases, Perforated—Three Cases Nonperforated—Two Cases Nonperforated with Acute Pancreatitis—One Case*

	Perforative	Per Cent	Nonperforative	Per Cent		Perforative	Per Cent	Nonperforative	Per Cent
Time					White blood cells				
12 hours	0	0	0	0	16,000 +	2	67*	3	100*
24 hours	1	33	0	0	16,000 —	1	33	0	0
48 hours	1	33	2	67	Polymorphonuclears	2	67*	1	33
72 hours	0	0	0	0	80% +	1	33	2	67
96 hours	1	33	0	0	80% —	0	0	1	33
96+ hours	0	0	1	33	Mild	2	67	1	33
Nausea +	3	100	3	100	Moderate	1	33	1	33
Nausea 0	0	0	0	0	Severe	0	0	0	0
Vomiting +	3	100	3	100	1 to 20 years	0	0	0	0
Vomiting 0	0	0	0	0	21 to 40 years	0	0	2	67*
Chill +	0	0	0	0	40+ years	3	100*	1	33
Chill 0	3	100*	3	100*	Fluid				
Fever +	3	100	3	100	Little	1	33	0	0
Fever 0	0	0	0	0	Much	2	67	3	100
Diarrhea +	0	0	0	0	Clear	0	0	0	0
Diarrhea 0	0	0	2	100	Turbid	2	67	3	100
Constipation +	1	100	0	0	Thick	1	33	0	0
Constipation 0	0	0	2	100	Sinear (forms)				
Obstipation +	0	0	0	0	?	2	0	0	0
Obstipation 0	1	100	2	100	0	1	100	3	100
Quadrant 1	0	0	1	33*	1	0	0	0	0
Quadrant 2	0	0	2	67*	Bacteria (growth)				
Quadrant 3	2	67*	0	0	0 species	0	0	3	100*
Quadrant 4	1	33*	0	0	1 species	0	0	0	0
Tenderness +	3	100	3	100	2 species	2	67*	0	0
Tenderness 0	0	0	0	0	3 species	1	33*	0	0
Rigidity +	3	100	3	100	4 species	0	0	0	0
Rigidity 0	0	0	0	0	5 species	0	0	0	0
Rebound tenderness +	1	100	1	50	6 species	0	0	0	0
Rebound tenderness 0	0	0	1	50	B coli	3	100*	0	0
Distention +	3	100	0	0	Green streptococcus	2	67*	0	0
Distention 0	0	0	1	100	C welchii	1	33*	0	0
Mass +	1	33	0	0	Sequelae 0	0	0	2	67*
Mass 0	2	67	3	100	1 to 3	0	0	1	33*
Pelvic signs +	1	33	0	0	4 to 7	3	100*	0	0
Pelvic signs 0	2	67	2	100	Recovered	0	0	3	100*
					Died	3	100*	0	0

patient was mildly ill. The three patients without perforative lesions recovered without important sequelae. In all of these, the smear showed no organisms, and the cultures yielded no growth. All three of the patients with perforative lesions died with four or five complications and all showed two or more organisms. *B coli* was present in all three cases with the green streptococcus in two and the nonhemolytic streptococcus in one. *C welchii* was present with *B coli* and the green streptococcus in one case.

Comment on Lesions of the Gallbladder—Here the difference between the perforative and nonperforative lesions is striking. The leakage of bile into the peritoneal cavity is not without danger even if it is sterile, and in large amounts it may result in death. This has been demonstrated in laboratory animals by Horrall³⁴ and others. Small doses of nonpathogenic organisms may prove lethal if small quantities of bile are present. Likewise, it has been demonstrated that sterile bile in the peritoneum may produce a chemical peritonitis of such a degree that bacteria will pass through the wall of an intact intestine in experimental animals. One of these cases seems to illustrate this fact. Cholecystostomy was done, and the bile was reported to be sterile. Some of it leaked into the abdominal cavity and caused peritonitis. The peritoneal exudate at the time of the second operation yielded three different species of intestinal bacteria.

MISCELLANEOUS CASES

In the miscellaneous group, the individual cases of particular interest were (1) the case of fulminating hemolytic streptococcic idiopathic peritonitis starting with a sore throat and (2) the cases of late puerperal fever. The blood culture in the former was sterile, and it is a question whether the spread to the peritoneum was via the intestine or via the retroperitoneal lymphatics. Either of these routes seems more logical than the hematogenous route usually considered for these cases. The case of low grade puerperal fever illustrates a point with regard to anaerobes. The disease had lasted over a month, and the hemolytic streptococcus was presumably of low grade virulence. When first recovered from the peritoneal fluid, it would not grow aerobically on the blood agar plates. It was only after several transplants in meat medium that it would grow aerobically. This evidently illustrates a law that streptococci which have grown for some time in environment without air come to prefer an anaerobic environment. This is seen frequently in abscesses of the brain or lungs and is probably true of many of the intestinal streptococci and possibly of other organisms as well.

A CONSIDERATION OF THE DATA FROM THE POINT OF VIEW OF THE NATURE AND EXTENT OF THE PERITONEAL INVOLVEMENT

ACUTE LOCAL PERITONITIS

There are forty-seven cases in this group, 83 per cent of which were due to appendicitis. The cases are summarized with the other groups

³⁴ Horrall, O. H. Experimental Bile Peritonitis. Its Treatment in the Dog, Arch. Int. Med. **43** 114 (Jan.) 1929.

in table 8 We wish to call particular attention to the following facts More than three fourths of the patients came to the hospital within forty-eight hours, and of the appendicitis group, two thirds came in within twenty-four hours Over three fourths of the patients with appendicitis gave a typical history of that disorder, which is taken to be a generalized abdominal or epigastric pain gradually localizing in the right lower quadrant Signs were usually present in only one quadrant The blood count ranged high None of the patients with appendicitis and only one of the others appeared seriously ill, and complications were mild Two thirds of the patients had no sequelae All of them recovered Almost two thirds of this group went home within fifteen days The peritoneal exudate was generally not profuse It was usually turbid but without odor In one third of the cases no smear of the fluid was made, of the others almost three fourths showed no organisms In two thirds of the cases the peritoneal fluid yielded no growth in culture, but in one third organisms were present, six of them containing four different species and one containing five In the seventeen cases of this series showing organisms, nonhemolytic *B coli* was the commonest species found, being present in thirteen, *C welchii* was next with seven cases, and the green streptococcus was present in five

ACUTE DIFFUSE PERITONITIS

This group contains thirty-six cases and differs strikingly from the preceding and succeeding groups in many respects (table 8) The patients did not come to the hospital so early, although the symptoms of nausea, vomiting, chills and fever were more severe Two thirds of the patients with appendicitis in this group gave a typical history of pain This does not correspond exactly to the patients who came to the hospital early In sharp contradistinction to the other groups, over three fifths of these patients had abdominal signs in all four quadrants The total white blood count was frequently low in this group, but the polymorphonuclear count was high None of these cases was considered mild Three fifths of them were considered moderately severe and two fifths were markedly severe All but one fourth of the patients had postoperative complications, some as many as seven A third of the patients died, and practically all of the others had a long stay in the hospital In a great majority of the cases there was a large quantity of peritoneal exudate, either turbid or thick, although in two thirds of the cases it was without odor Smears of the peritoneal fluid were made in thirty-one cases No organisms were seen in 29 per cent while one or more forms were visible in 71 per cent In five of these cases the fluids yielded no growth, but in the others it yielded one or more species In one case there were no less than six different species Nonhemolytic *B coli* was present in twenty-nine or 94 per

cent, of the thirty-one fluids yielding growth. The green streptococcus was second with 58 per cent, both of these being more common in the cases of appendicitis than in the other cases. *C. welchii* was third with 39 per cent, but was much more common in the other cases than in the appendicitis group. A nonhemolytic streptococcus was also present in more than one fourth of these cases.

TABLE 8—Analysis According to Extent of Peritoneal Involvement—One Hundred and Six Cases

	Acute Local Peritonitis		Acute Diffuse Peritonitis		Abscess			Acute Local Peritonitis		Acute Diffuse Peritonitis		Abscess	
	No	%	No	%	No	%		No	%	No	%	No	%
Appendicitis	39	85*	17	47*	20	87*	White blood cells	27	64*	18	55*	12	60*
Other	8	17*	19	33*	3	13*	16,000 +	15	36*	15	45*	8	40*
Total	47		36		23		16,000 —	29	72*	22	85*	11	58*
Time							Polymorphonuclears	11	28*	4	15*	8	42*
12 hours	8	17*	4	11*	1	4	80% +	26	75*	0	0	6	26
24 hours	17	36*	12	33*	0	0	80% —	20	43	21	59*	14	61*
48 hours	12	24*	6	17*	2	13	Mild	1	2	15	41	1	1
72 hours	4	8	4	11*	5	13*	Moderate	18	38*	9	25	7	30
96 hours	2	4	3	8*	4	17*	Severe	19	41*	9	25	5	22
96+ hours	3	6	7	19*	13	56*	1 to 20 years	10	21	18	50*	11	45*
Nausea +	37	77	29	88	20	87	21 to 40 years						
Nausea 0	10	23	4	12	3	13	40+ years						
Vomiting +	30	67	29	85	20	87	Fluid						
Vomiting 0	15	33	5	15	3	13	Little	38	81*	9	25	4	17
Chill +	3	16	6	32	5	38	Much	9	19	27	75*	19	83*
Chill 0	16	84	13	68	8	62	Clear	9	19*	0	0	0	0
Fever +	38	81	34	94	23	100	Turbid	36	77*	28	76*	6	26
Fever 0	8	19	2	6	0	0	Thick	2	4	8	22*	17	74*
Typical	30	77*	11	65*	13	65*	Smear (forms)						
Atypical	9	23*	6	37*	7	35*	?	15		5		3	
Diarrhea +	4	11	6	21	0	0	0	23	72*	9	29	2	10
Diarrhea 0	32	89	22	79	18	100	1	5	16*	6	19*	0	0
Constipation +	14	40	17	50	7	37	2	3	9	9	29*	9	45*
Constipation 0	23	60	15	50	12	63	3	1	3	7	23*	9	45*
Obstipation +	3	9	4	11	0	0	Bacteria (growth)						
Obstipation 0	31	91	26	87	19	100	0 species	30	64*	5	14*	0	0
Quadrant 1	20	64*	4	11	14	61*	1 species	4	9	5	14*	2	9
Quadrant 2	13	28	5	14	6	26	2 species	3	6	5	14*	6	26*
Quadrant 3	2	4	5	14	1	4	3 species	3	6	6	17*	6	26*
Quadrant 4	2	4	22	61*	2	9	4 species	6	13	10	28*	3	13*
Tenderness +	47	100	35	100	23	100	5 species	1	2	4	11*	4	17*
Tenderness 0	0	0	0	0	0	0	6 species	0	0	1	3*	2	9
Rigidity +	29	64	32	97	14	78	B. coli	13	28*	27	75*	22	96*
Rigidity 0	16	36	1	3	4	22	Green streptococcus						
Rebound tenderness +	25	76	16	83	5	55	C. welchii	5	11*	15	42*	15	65*
Rebound tenderness 0	8	24	3	16	4	47	Sequelae 0	6	13*	11	31*	10	44*
Distention +	5	19	18	72	8	54	1 to 3	28	60*	8	24	11	48*
Distention 0	21	81	7	28	7	46	4 to 7	18	38*	14	42*	8	35*
Mass +	3	8	3	12	16	76	Days 15—	1	2	12	36*	3	13
Mass 0	35	92	23	88	5	24	Days 16+	29	62*	9	25	3	13
Pelvic +	24	59	17	55	13	62	Recovered	18	38	27	75*	20	87*
Pelvic 0	17	41	14	45	8	38	Died	47	100	24	67	19	83
								0	0	12	33*	4	17*

PERITONEAL ABSCESS

This group, which is composed of twenty-three cases, has several striking features of its own (table 8). The first is the duration of symptoms before hospitalization, more than one half of the cases appearing after four days. Chill was present in more than one third of the cases in which this symptom was noted. The percentage of cases with a typical history was almost exactly the same as in the cases of diffuse peritonitis. As with the first group, the large majority of cases had

signs limited to one or two quadrants. One fourth of the cases in this group were considered to be mild, one eighth severe, while three fifths fell into the intermediate group. Half of the patients had no sequelae, but some of the rest had as many as four different complications, and four of them died. All who survived were in the hospital a long time. The peritoneal fluid was generally present in considerable quantity and was thick. In over 80 per cent, it had a foul or fecal odor. In three cases a smear was not made, of the other twenty, two showed no organisms, but in all of the others, 90 per cent, more than one form was seen in the smear. Every one of these fluids yielded bacterial growth and only two contained a single species, both of these being from cases of appendicitis. The others all showed multiple species, two of them as many as six different kinds. As with the other two groups, the non-hemolytic *B. coli* takes first place, being present in every case but one. The green streptococcus was present in two thirds of the cases and the hemolytic *C. welchii* in almost 40 per cent.

Comment on the Data from the Standpoint of the Extent of Peritoneal Involvement—There seems to be a definite relationship between the duration of symptoms before admission and the extent and nature of the peritoneal involvement. The fact that there was a higher percentage of typical histories may have been a factor in bringing the patients in the group with acute local peritonitis to the hospital earlier than the others, but earlier arrival did not correspond with the typical history, and in order that we may have an adequate answer to the question of why patients do not come to the hospital earlier we must go deeper into human reactions to the idea of hospitalization, the reactions of both the family physician and the patient. The earlier age incidence in the first group may explain to a certain degree the early admission to the hospital, or it may indicate the reason for a greater degree of resistance against the infection on the part of the patient. The quadrant signs and the severity of the symptoms, the sequelae and the mortality all correspond to the extent of the inflammation and are to be expected. On the other hand, the turbidity of the peritoneal fluid, the number of organisms seen in the smear and the number of species recovered are greater in the cases of abscess than in the cases of acute diffuse peritonitis, and the three common organisms, *B. coli*, green streptococcus and *C. welchii*, increase in frequency as one passes from the acute local to the acute diffuse and then to the abscess group. The relation of the incidence to the mortality in these three groups is shown graphically in chart 1. Here of course other factors offset the factor of bacterial numbers, namely, the limitation of the area of absorption, the limitation of the effective range of activity of the bacteria and the minimal interference to the function of the intestine, all of which render the cases of abscess more benign.

CONSIDERATION OF THE DATA FROM THE POINT OF VIEW OF THE
ORGANISMS SEEN IN OR CULTIVATED FROM THE
PERITONEAL EXUDATE

STAINED SMEARS OF THE PERITONEAL EXUDATE

Smears were made in eighty-three of the cases in this series, but were omitted in twenty-three examinations usually when the specimens were small in quantity and taken on cotton swabs. No attempt was made to classify the organisms seen on the slide other than to group

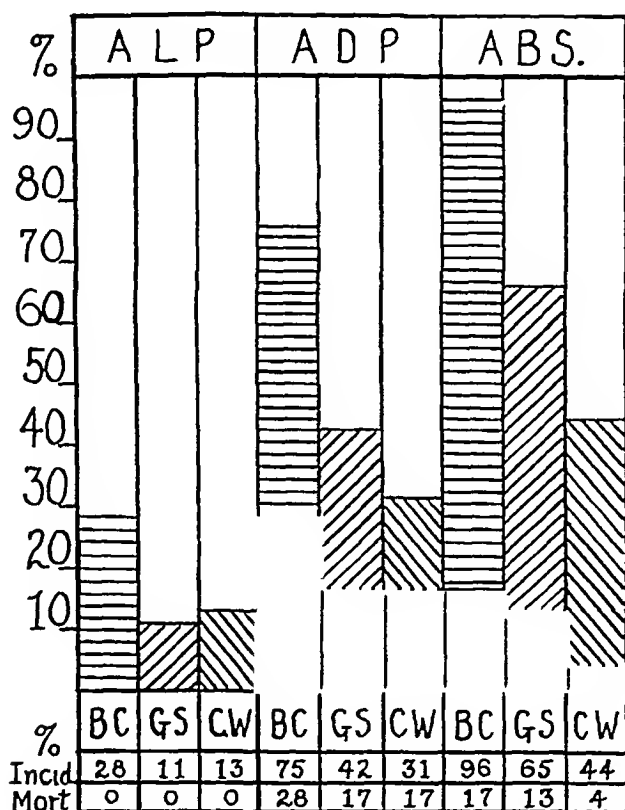


Chart 1—Incidence and mortality of *B. coli*, green streptococci and *C. welchii* in the three main peritonitis groups. *ALP* indicates acute local peritonitis, *ADP*, acute diffuse peritonitis, *ABS*, abscess. The shaded area indicates the percentage of patients who survived, the solid area, the percentage who died.

them into cocci or bacilli and to note whether or not they retained the gentian violet of the Gram stain, because it is absolutely impossible to classify more accurately organisms which are present in exudate the pleomorphic and the degenerated forms, making a single species appear like several and the identical appearance of different species making many species appear as one. We cannot be sure therefore in many cases whether or not we cultivated all of the organisms that we saw, but this rough differentiation in the comparison of smear and

culture seems to have been profitable. In correlating the smears with the final cultures, it is found that they fall into four groups, which will be analyzed to determine, if possible, whether they bear any relationship to the symptoms and signs presented or have any prognostic significance (table 9).

Cases Showing No Organisms on Smear and Yielding No Growth—Twenty-five cases fell into this group, seventeen of which were due to appendicitis. Over 80 per cent of the patients came to the hospital within forty-eight hours and 60 per cent within twenty-four. Eighty

TABLE 9—*Analysis of Certain Important Data with a Correlation of Smears with Growth of Bacteria from the Peritoneal Fluid*

	SO = GO		S > G		S < G		S+ = G+	
	No	%	No	%	No	%	No	%
Total	25		7		24		27	
Time								
12 hours	7	28*	0	0	4	17*	1	4
24 hours	8	32*	0	0	7	29*	4	15*
48 hours	6	24*	1	14*	3	13*	5	19*
72 hours	1	4	2	29*	3	13*	5	19*
96 hours	0	0	1	14*	3	13*	3	11*
96+ hours	3	12	3	43*	4	17*	9	33*
Quadrant 1	13	52*	7	100*	7	29*	6	22*
Quadrant 2	8	32*	0	0*	6	25*	5	19*
Quadrant 3	3	12	0	0	2	8*	2	7*
Quadrant 4	1	4	0	0	9	38*	14	52*
Mild	14	56*	1	14*	4	17	5	18
Moderate	10	40*	6	86*	15	62*	11	41*
Severe	1	4	0	0	5	21*	11	41*
Sequelae 0	18	72*	5	72*	4	17	12	46*
1 to 3	7	28	1	14	13	57*	10	38*
4 to 7	0	0	1	14	6	26*	4	15
Recovered	25	100*	7	100*	19	79	20	74
Died	0	0	0	0	5	21*	7	26*
Fluid								
Little	19	76*	0	0	8	33	6	22
Much	6	24	7	100*	16	67*	21	78*
Clear	7	28	0	0	0	0	0	0
Turbid	18	72*	1	14	14	58*	14	52*
Thick	0	0	6	86*	10	42*	13	48
Odor								
None	20	100*	1	20	14	77*	7	31
Foul	0	0	3	60*	1	6	9	39*
Fecal	0	0	1	20	3	17	7	26*

per cent of the cases of appendicitis had a typical history. Gastric and intestinal symptoms were minimal. On physical examination, over half of the cases had signs limited to one quadrant, and in 84 per cent they were limited to one or two. The total white cell count was usually high, with polymorphonuclears relatively low, indicating a good resistance against a mild infection. Over one half of the patients were considered to be only mildly ill on admission to the hospital, and all but one of the rest were only moderately ill. All of these patients recovered, 72 per cent had no sequelae and the rest only a few. The great majority left the hospital within fifteen days. In three fourths of the cases the fluid was small in quantity. In one fourth it was described as being clear in the rest turbid and in none thick. In all of the cases recorded (twenty) there was no odor.

Cases Showing Forms on Smear, Some of Which Did Not Grow Out—This is a small group of seven cases, and the figures are therefore less reliable than in the other groups. Six of the cases were due to appendicitis, and in five an abscess had formed. Four of the smears showed gram-positive cocci with gram-negative bacilli, and the cocci failed to grow. One showed cocci with both gram-positive and gram-negative bacilli, and the cocci failed to grow. Two showed gram-positive bacilli, together with gram-negative bacilli and gram-positive cocci. The gram-positive bacilli failed to grow. These patients were all late arrivals at the hospital. Three of five had chills. In every case the signs were limited to a single abdominal quadrant. In four of five cases distention was recorded. In six of the seven, a mass was felt. None of the patients was judged to be severely ill on admission. One was mildly, and the rest moderately, sick. All of the patients recovered, and only one had serious complications. Five had no sequelae, although all of them were in the hospital for more than fifteen days. The peritoneal fluid in all of these cases was present in considerable quantity, in all but one it was thick, and in four of five it was odoriferous.

Cases in Which the Peritoneal Fluid Yielded Growth of Organisms Which Did Not Appear on Smear—This group consists of twenty-four cases, fourteen of which were due to acute appendicitis. In this group the arrival at the hospital was fairly evenly distributed over the time periods, a little over half coming in within forty-eight hours. Seventy-one per cent of the cases of appendicitis had a typical history. On physical examination, only a little over one fourth of the cases had signs limited to a single quadrant, and in three eighths of them four quadrants were involved. Tenderness was constant, rigidity was more frequent than in the preceding group, and the rebound sign was present in about four fifths of the cases when this symptom was recorded. Distention was present in 60 per cent. Total blood counts were low in half of the cases, but the polymorphonuclear percentage relatively high, indicating, perhaps, an increased severity of the infection. Only one sixth of the patients were mildly ill on admission and more than one fifth were considered to be seriously ill. Twenty-one per cent of the patients died, only a sixth were without sequelae, and over one fourth had serious and numerous complications. All who recovered were in the hospital more than fifteen days. The peritoneal fluid was in considerable quantity in two thirds of the cases, turbid in a little over half and thick in the remainder, but no odor was noted in three fourths of the cases.

Cases Showing All of the Forms in the Smear Which Later Appeared in Culture—There were twenty-seven in this group, twenty-

two of which were due to appendicitis. Sixty-three per cent of the patients came to the hospital after forty-eight hours. Nausea and vomiting were frequent, and fever was invariably present. In a third of the cases recorded there was a history of chill. Only 59 per cent of the cases of appendicitis had a typical history. On physical examination more than half of these patients showed signs in all four quadrants. Blood counts tended to be low, and the polymorphonuclear percentage corresponded. Forty-one per cent of the patients were judged to be seriously ill on admission to the hospital, and as many more were moderately ill. Only five of the cases were mild. Twenty-six per cent died, although the complications were somewhat less frequent than in the preceding group. The peritoneal fluid was in general more profuse, thicker and much more often odoriferous than in the preceding group.

Comment on the Correlation of Smears of Peritoneal Fluid with Growth of Bacteria—The first group, in which both smear and growth are negative evidently represents a condition in which the infecting agents although sufficiently active in the wall of the organ to call forth a peritoneal reaction and exudation, had not entered the peritoneal cavity in great numbers or multiplied sufficiently to be seen in the smear. The peritoneum was in control of the situation. The symptoms were mild, the sequelae were few, and when the distributing focus was removed all of the patients promptly recovered. The second group is small and the figures are therefore unreliable, but a general principle is brought out which we believe to be of value. Organisms appeared on smear which failed to grow out. Failure to grow indicated either that they were dead or could not multiply in our culture mediums. If they were dead, they were either killed by the action of the peritoneum or its fluid or died in transit to the laboratory. We know that several of the specimens in this group were planted immediately, and we believe that the organisms were probably destroyed in the peritoneal fluid which would suggest a resistance on the part of the body to this particular element of the infection. The bactericidal action of these fluids might be subject to experimental demonstration. Runeberg²⁰ found that it had bactericidal action to a certain degree. In the third group organisms grew out which did not appear in the smear. These were viable organisms present in small numbers which were capable of multiplying and potentially able to take part but as yet not actively taking part in the production of symptoms. In the last group all of the organism forms seen in the smear were viable and recoverable. Presumably they were active had already gained a foothold had been multiplying and had already produced symptoms. Some at least were likely to continue to produce symptoms after the removal of the distributing focus. We believe that if smear and culture are correlated

in every case, the study will be a fair basis for prognosis. If the case falls into the first two groups the prognosis will be good, if into the third, prognosis must be guarded and depend on special features of the individual case with serious consequences expected in a certain proportion of the cases, if into the fourth group still more trouble is to be expected.

CULTURES FROM THE PERITONEAL EXUDATE

Our series of cases may be conveniently divided into three groups from the point of view of bacterial growth: those yielding no growth, those yielding from one to three species and those yielding from four to six species. The results are summarized in table 10.

Cases Yielding No Growth—This group comprises thirty-five cases, three fourths of which were due to appendicitis and the rest to other lesions (table 10). Thirty of these cases were classed as acute local peritonitis and five as acute diffuse peritonitis. There were no cases of peritoneal abscess which failed to yield bacterial growth. We wish to emphasize particularly the following points: Eighty-three per cent of the total number and 92 per cent of the patients with appendicitis came to the hospital within forty-eight hours. Eighty-one per cent of the cases of appendicitis gave a typical history of pain. On physical examination signs were generally limited to two quadrants, in over one half of the cases the signs were present in only one quadrant. Tenderness was constant, but the rebound sign and rigidity was found in not more than three fourths of the cases. Distention was minimal, no masses were felt, but pelvic tenderness was present in over one half of the cases. The blood count was fairly high in three fourths, and the percentage of polymorphonuclears corresponded. The general impression of the severity of these cases on admission placed 60 per cent in the moderate class. Only one patient was considered to be severely ill. Every patient survived, sequelae were absent or minimal. Over three fourths of the patients left the hospital within fifteen days. The fluid was generally small in quantity, clear or turbid, but never thick. In no case in which this item was recorded was there any odor.

Cases Yielding From One to Three Species of Bacteria—This group includes forty cases of which, as in the first group, three fourths were due to appendicitis (table 10). On the other hand, only ten of these were classed as acute local peritonitis while sixteen were called acute diffuse peritonitis, and fourteen were localized peritoneal abscesses. Only a little over one half of these patients came to the hospital within forty-eight hours of the onset of the illness. Fever was almost invariably present and chill was a fairly common symptom being present in half of the cases of appendicitis in which it was mentioned while nausea and vomiting were considerably more frequent than in

TABLE 10—*Analysis of Data from the Point of View of the Growth of Organisms from Peritoneal Exudate—One Hundred and Six Cases*

	Growth 0		Growth 1 to 3 Species		Growth 4 to 6 Species			Growth 0		Growth 1 to 3 Species		Growth 4 to 6 Species	
	No	%	No	%	No	%		No	%	No	%	No	%
Total	35		40		31		Rebound tender						
Acute local peritonitis	30	87*	10	25	7	23	ness +	18	75*	21	87*	15	71*
Acute diffuse peritonitis	5	13	16	40*	15	48*	Rebound tender-ness 0	6	25	3	13	6	20
Abscess	0	0	14	35*	9	29*	Distention +	2	12	13	48*	19	68*
Time							Distention 0	15	88*	14	52	9	32
12 hours	7	20*	4	10*	2	6*	Mass +	0	0	13	41*	9	35
24 hours	12	34*	10	25*	7	22*	Mass 0	28	100*	19	59*	17	63*
48 hours	10	29*	7	18*	3	10*	Pelvic +	17	57	22	69*	17	57
72 hours	1	3	6	15*	5	16*	Pelvic 0	13	43*	10	31	13	43*
96 hours	0	0	2	5*	6	19*	White blood cells						
96+ hours	5	14	11	28*	8	26*	16,000 +	24	73*	23	62*	13	47
Nausea +	26	74*	32	89*	28	90*	16,000 —	9	27	14	38	15	53
Nausea 0	9	26	4	11	3	10	Polymorphonuclears						
Vomiting +	22	63*	30	81*	28	90*	80% +	23	72*	22	63*	19	73*
Vomiting 0	12	34	7	19	3	10	80% —	9	28	13	37	7	27
Chill +	1	8	10	41*	3	21	Mild	21	60*	7	18	4	13
Chill 0	12	92*	14	59	11	79*	Moderate	13	37	24	60*	18	58*
Fever +	28	82*	38	94*	28	94*	Severe	1	3	9	22	9	29
Fever 0	6	18	1	3	2	6	Sequelae 0	24	69*	15	39*	7	25
Diarrhea +	3	11	4	14	3	12	1 to 3	11	31	14	37*	14	50*
Diarrhea 0	24	89	24	86	22	88	4 to 7	0	0	9	24*	7	25
Constipation +	9	32	12	36	15	57	Days 15—	27	77*	10	26	4	13
Constipation 0	19	68*	21	63*	11	43*	Days 16+	8	23	29	74*	27	87*
Obstipation +	1	4	1	3	5	19	Recovered	35	100*	31	78	24	77
Obstipation 0	26	96*	32	97*	21	81*	Died	0	0	9	22*	7	23*
Quadrant 1	20	57*	18	45*	10	32*	Fluid						
Quadrant 2	11	31*	4	10*	9	30*	Little	27	77*	15	37	9	29
Quadrant 3	3	3	9	10*	1	3*	Much	8	23	25	63*	22	71*
Quadrant 4	1	3	14	35*	11	35*	Clear	9	26*	0	0	0	0
Tenderness +	35	100	40	100	31	100	Turbid	26	74	27	68*	15	48
Tenderness 0	0	0	0	0	0	0	Thick	0	0	13	32	16	52*
Rigidity +	24	71*	29	85*	22	76*	Odor 0	24	100*	17	61	8	33
Rigidity 0	10	29	5	15	7	24	Foul	0	0	5	18*	8	33*
							Fecal	0	0	6	21*	8	33*

	Growth Number of Species 1 to 3		Growth Number of Species 4 to 6	
	Number Per Cent		Number Per Cent	
	40		31	
Total number of cases				
Anaerobes				
Hemolytic C welchii	6	15*	21	68*
Nonhemolytic C welchii	0	0	4	13
Other spore formers	2	5	4	13
Gram + B nonspore formers	2	5	4	13
Gram — B nonspore formers	0	0	3	10
Gram + cocci	5	13*	6	19*
Gram — cocci	0	0	1	3
Aerobes				
Hemolytic B coli	10	25	10	32
Nonhemolytic B coli	32	80*	30	97*
Green streptococci	14	35*	21	68*
Hemolytic streptococci	4	10	1	3
Nonhemolytic streptococci	9	23*	6	19
Diphtheroid	3	8	8	26*
B proteus	0	0	6	19*
B subtilis	1	3	1	3
B proteococcus	0	0	1	3
B prodigiosus	0	0	1	3
B mucosus capsulatus	0	0	1	3
Staphylococcus albus	1	3	2	6
Staphylococcus aureus	0	0	2	6
Staphylococcus citreus	0	0	1	3
Leptothrix	0	0	1	3

the first group In only two thirds of the cases of appendicitis in this group was there a typical history of that disorder In the majority of the cases the signs were present in more than one quadrant Tenderness was invariably present, and rigidity and rebound tenderness in from 85 to 87 per cent of the cases About one half of the patients showed distention The blood counts were generally a little lower in this group than in the preceding Only one fifth of the cases were considered mild and almost one fourth were severe Twenty-two per cent of the cases were fatal Complications occurred in two thirds of the cases The peritoneal fluid was present in considerable quantity in almost two thirds of these cases, and in one third it was thick In two fifths of the cases in which odor was noted, the fluid had a foul or fecal odor Only eleven of these cases yielded a single species of bacteria, fourteen showed two species and fifteen three Nonhemolytic *B coli* was found in 80 per cent and the hemolytic variety in 25 per cent The green streptococcus was recovered in 35 per cent, the nonhemolytic streptococcus in 23 per cent *C welchii* was present in only 15 per cent Anaerobic streptococci, hemolytic diphtheroid bacilli, *B subtilis*, *Staphylococcus albus* and certain nonpathogenic spore-forming anaerobes were present in scattered cases

Cases Yielding From Four to Six Species—There were thirty-one cases in this group, two thirds of which were due to appendicitis (table 10) Seven of these cases were classed as acute local peritonitis, fifteen as acute diffuse and nine as abscess Almost two thirds of these patients came to the hospital after forty-eight hours Nausea, vomiting and fever were present in over 90 per cent of the cases, but chill was not frequent More of these cases gave a typical history than those in the two preceding groups Less than one third had signs limited to one quadrant Distention occurred in 68 per cent Blood counts were generally low, with a relatively high polymorphonuclear percentage Only four of these cases were considered mild on admission, and almost a third were severe Twenty-two percent of the patients died, exactly the same percentage as in the preceding group, but the complications were more frequent, and the stay of the patients in the hospital was longer than in the cases in the second group The peritoneal fluid was more frequently profuse and thicker than in the preceding class, and in two thirds of the cases it was recorded as malodorous Four species were cultivated from the peritoneal fluid from nineteen of these cases, five species from nine and six from three Nonhemolytic *B coli* was present in all but one of these cases (a high intestinal perforation) The hemolytic variety was found in 32 per cent The green streptococcus occurred in 68 per cent and *C welchii* in the same number, while other bacteria occurred in considerably fewer numbers A graph

showing the numerical incidence of bacterial species in the cases of appendicitis is given in chart 2

Discussion of the Data from the Standpoint of Bacteria Grown from the Peritoneal Exudate—It is evident that in the great majority of cases yielding no growth, the disease is limited to the region of the focus of infection. The peritoneum is in control of the situation, and the organisms, if present, are not viable. With viable organisms present it is not unexpected to find either a diffuse process or a more extensive local process. As one would expect, the duration of symptoms in the group of cases yielding no growth was short, while it was distributed widely in other groups. The symptoms of nausea, vomiting, constipation and obstipation, the physical signs of quadrant involvement and distention

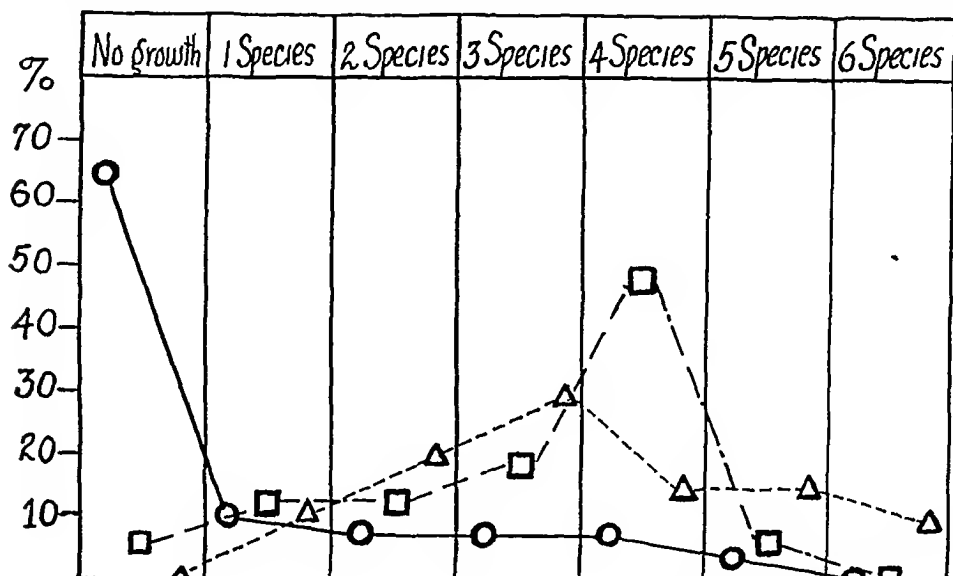


Chart 2—Curves showing the number of different species of bacteria in the peritoneal exudates of seventy-six cases of appendicitis: acute local peritonitis, thirty-nine cases; acute diffuse peritonitis, seventeen cases; abscess, twenty cases. The circles indicate the cases of acute local peritonitis, the squares, acute diffuse peritonitis, the triangles, abscess.

the white blood cell count, the estimate of severity, the sequelae and the duration of stay in hospital all show progressive changes corresponding to the number of species present in the peritoneal fluid. In certain other respects, namely, in the matter of chill, fever, rigidity, rebound tenderness, mass, pelvic signs and percentage of polymorphonuclears, one finds that in our series, the group with from one to three species gives evidence of being more powerfully affected than the group with from four to six, and when it finally comes to the percentage of fatal cases, the figures are practically the same. This is all the more interesting when we consider that the low mortality of the group with

one species brings down the average of the group with from one to three species. Although this summary seems to show a definite causative relationship between the presence of organisms and the severity of the infection, it is of interest that in our series of cases the reaction of the patients to the presence of from four to six species is not much greater than their reaction to the presence of from one to three species. This cannot be explained on the basis of abscess formation, because as a matter of fact in our series there was a greater proportion of abscesses in the second group. It seems to us that there are at least two possible explanations. Beyond three species the organisms are indifferent, without effect and simply saprophytic in the exudate, or with respect to certain symptoms so indicated they are actually antagonistic to the effects of the other organisms with which they are living. They may be antagonistic to certain activities of the other species and protagomistic to others. It is well known that within the intestinal canal various organisms have adjuvant and others inhibiting effects on the activities of their fellow species.

In turning to that portion of the table which lists the species found, one is struck by the prominence of three species, namely, nonhemolytic *B coli*, green streptococcus and *C welchii*. In the group with from one to three species, the nonhemolytic streptococcus is also frequent, but when it is remembered that this group merges with the green, its identity is not sufficiently distinct to lay much stress on it. This is less frequent in the group with from four to six species while the green streptococcus increases almost twofold and the *C welchii* increases over fourfold. One may be surprised that this fourfold increase of *C welchii* does not increase the severity and mortality of this group, but this is quite consistent with the observations with regard to this organism in previous summaries made earlier in this paper and adds to the evidence everywhere consistent that this organism is not as serious a factor in peritonitis as it has been considered to be.

GROUPING OF CASES ACCORDING TO CERTAIN SPECIES FOUND IN THE PERITONEAL EXUDATE

It is evident from the preceding summaries that the most frequent organisms found in our series were (1) nonhemolytic *B coli*, (2) green streptococcus and (3) *C welchii*. Others of secondary importance were (1) hemolytic *B coli* (which was never found without the nonhemolytic type being present also), (2) nonhemolytic streptococcus (which, as we have already stated, merges into the green group), (3) anaerobic streptococcus (which in turn merges into the non-hemolytic group), (4) nonhemolytic *C welchii* (which was never found without the hemolytic type being present also) and (5) diphtheroid bacilli, both aerobic and anaerobic (small gram-positive nonspore-

formers) There is a sufficient number of cases in which the first three organisms were found to warrant grouping, but it must be emphasized that because of the frequency of concurrence, these groups overlap, and certain cases are common to two or all three groups. The comparison may be seen in table 11.

Cases Yielding Nonhemolytic B coli—Of the seventy-one cases in the series in which bacteria were found in the peritoneal exudates, sixty-two, or 87 per cent, yielded nonhemolytic *B coli*, forty-six of these cases

TABLE 11—Analysis of Important Data from Cases Yielding *B. Coli* or Green *Streptococcus* or *C. Welchii*

	B coli						Green Streptococcus						C welchii								
	Appen dicitis			Others			Appen dicitis			Others			Appen dicitis			Others			Total		
	No		%	No		%	No		%	No		%	No		%	No		%	No		%
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	
Totals	46		16		62		24		11		35		15		12		27				
Typical	29	63					15	63					8	53							
Atypical	17	37					9	37					7	47							
Quadrant 1	22	48	4	25	26	42*	9	37	3	27	12	34*	6	40	3	25	9	33*			
Quadrant 2	10	22	1	6	11	18*	5	21	2	18	7	20*	5	33	2	17	7	26*			
Quadrant 3	2	4	2	13	4	6*	1	4	1	9	2	6	0	0	0	0	0	0			
Quadrant 4	12	26	9	56	21	34*	9	37	5	45	14	40*	4	27	7	58	11	41*			
W. B. C.																					
16,000 +	25	60	6	43	31	55*	13	52	4	40	17	51	8	57	4	36	12	48*			
16,000 —	17	40	8	57	25	45*	8	38	6	60	14	45*	6	43	7	64	13	52*			
Polymorpho nuclears																					
80% +	27	66	9	69	36	67*	14	70	4	45	18	62*	10	77	5	56	15	68*			
80% —	14	34	4	31	18	33	6	30	5	55	11	38	3	23	4	45	7	32			
Mild	9	19	1	6	10	16*	4	17	2	18	6	17*	2	13	1	8	3	11*			
Moderate	28	61	7	44	35	57*	15	62	6	55	21	60*	9	60	4	33	13	48*			
Severe	9	19	8	50	17	27*	5	21	3	27	8	23*	4	27	7	58	11	41*			
Sequelae 0	19	42	1	7	20	34*	11	48	2	20	13	39*	4	27	1	9	5	19*			
1 to 3	18	40	7	50	25	42*	8	35	3	30	11	33	7	47	5	45	12	46*			
4 to 7	8	17	6	43	14	24*	4	17	5	50	9	27*	4	27	5	45	9	35*			
Recovered	40	87	8	50	48	77*	19	79	6	55	25	71*	13	87	6	55	19	73*			
Died	6	13	8	50	14	21*	5	21	5	45	10	29*	2	13	5	45	7	27*			
Fluid																					
Turbid	23	50	11	69	34	55*	9	37	8	73	17	49*	6	40	7	58	13	48*			
Thick	23	50	5	31	28	45*	15	63	3	29	18	51*	9	60	5	42	14	52*			
Odor																					
None	15	43	8	57	23	47	7	37	6	67	13	46	3	21	3	33	6	26			
Foul	11	31	2	14	1	26*	6	32	1	11	7	25*	6	43	2	22	8	35*			
Fecal	9	26	4	29	13	26*	6	32	2	22	8	29*	5	36	4	44	9	39*			

were due to acute appendicitis (table 11). A little over half of the patients came to the hospital after forty-eight hours. Nausea, vomiting and fever were present in over 90 per cent. Chill was a rather frequent symptom, being present in one fourth of the cases in which it was noted. Sixty-three per cent of the cases of appendicitis gave a typical history of that disease. In sixty per cent, the signs were limited to one or two quadrants. All of the patients had tenderness, four fifths, rigidity, three fourths rebound tenderness, and five eighths, distention. It is chiefly in this feature of distention that this group differs from the group without bacteria. Blood counts were elevated above 16,000 in only 55 per cent while two thirds had a polymorpho-nuclear percentage of over 80. About one sixth of these cases were

considered mild, and a little over one fourth were severe. About one fifth of the patients died, and almost all of those who recovered stayed in the hospital more than sixteen days. In two thirds of the cases there was a considerable amount of fluid, which was simply turbid in a little over one-half, but thick in the rest. In one half of the specimens, no odor was noted, but the rest were either foul or frankly fecal.

Cases Yielding Green Streptococci—Thirty-five or almost one half of the cases in our series that showed growth yielded green streptococci (table 11). In this group also a majority of the patients came to the hospital late. The percentage of histories of typical appendicitis was identical with that of the group yielding *B. coli*. There were fewer cases in the group in which a single quadrant was involved and more in which four quadrants were involved than in the series yielding *B. coli*. Otherwise the physical signs were very much the same. The total white cell counts were about the same, but the polymorphonuclear percentage was a trifle lower. The severity of the cases of this group is very similar to that of the preceding group, and although the complications were not so numerous there was a definitely higher mortality particularly in the cases of appendicitis. The quantity of fluid was usually greater and it was generally thicker, especially in the cases of appendicitis although the odor was not strikingly different.

Cases Yielding C. welchii—Twenty-seven cases yielded *C. welchii*, 38 per cent of the seventy-one specimens of peritoneal fluid (table 11). The patients came to the hospital a little later than those in the preceding two groups. The percentage of histories of typical appendicitis was definitely lower, which may have accounted for the delay in reaching the hospital. The extent of the abdominal signs tended to be a trifle greater, but this is not striking. Less than one half of the cases had a definitely raised total white blood count, but the polymorphonuclears were above 80 per cent in two thirds of the cases. One striking difference between this group and the two preceding is that on admission a much larger percentage of patients were considered seriously ill, although the mortality in this group was not higher than in the streptococcic group, and those who survived were not in the hospital any longer than those in the other groups. The quantity and consistency of the fluid were not markedly different but the odor was definitely noticed as being more offensive.

Discussion of Data from the Standpoint of the Three Common Bacterial Species—Table 11, which lists the important features of three groups containing *B. coli*, green streptococcus and *C. welchii*, is shown to demonstrate the uncertainty of drawing conclusions from groups of cases in which there are too many common factors. Fifteen cases yielded both nonhemolytic *B. coli* and the green streptococcus without

G welchii ten cases yielded *B coli* and *C welchii* without the green streptococcus, only one case yielded green streptococcus and *C welchii* without *B coli*, but sixteen cases yielded all three. The only suggestive points are the increased severity of symptoms, the increased number of sequelae and the increased odor to the peritoneal fluid in the cases yielding *C welchii*, but there is no increase in mortality. Similarly, inconclusive results are obtained when groups of cases are studied by comparing all of the cases yielding one of these organisms with all of the cases not yielding the given organism. There are too many concurrent organisms to get an idea of the effect of one. The most that can be said is that there seems to be some evidence that the presence of each of these organisms adds to the severity of the course of the disease. This seems to be somewhat more definite with respect to *C welchii* than with the others. It must be remembered, however, that when one of these organisms was absent, another or both of the others were present, thus increasing the importance of the opposing group. Perhaps the most logical conclusion that can be drawn from the data just presented is that each of these organisms plays a rôle but none of them is outstanding. The importance of any of these species in our series seems to depend more on its prevalence than on its outstanding virulence.

A COMPARISON OF CASES FROM THE POINT OF VIEW OF SYMBIOSIS

It is very difficult to evaluate the effect of any one organism, because when organisms are present, the great majority of cases have more than one species. Only eleven cases yielded a single organism, eight of these were nonhemolytic *B coli*, two were hemolytic streptococci and one an anaerobic diphtheroid. A hemolytic as well as a nonhemolytic *B coli* was cultivated in one other case. If this is grouped with the eight yielding pure cultures of nonhemolytic *B coli*, a small series of nine cases may be conveniently studied and compared with a series of twenty-six cases in which both *B coli* and some streptococci were present in symbiosis and these in turn with another series of twenty-two cases in which *B coli*, some streptococci and *C welchii* were present.

Cases Yielding Pure Cultures of B coli—Of the nine cases in this group eight were due to appendicitis and the other to volvulus. None of the patients came to the hospital within twelve hours and a little over half came after forty-eight hours. Nausea and vomiting were present in all but in one case there was no fever. Chills were rather common being present in half of the cases in which the symptom was noted. Three fourths of the cases of appendicitis give a typical history. Intestinal symptoms were minimal constipation the most frequent appearing in three of eight cases noted. On physical examination the signs were limited to one quadrant in seven of the nine cases. Tender-

ness was invariably present, but rigidity was considerably less frequent and rebound tenderness observed in only two cases. Distention was not a prominent feature. The white cell count was elevated in three fourths of the cases, with a corresponding increase in polymorphonuclears. Two thirds of the cases were placed in the moderate group with regard to severity, while two cases were considered mild and only one severe. All of these patients recovered, with relatively mild sequelae and complications, although they were all in the hospital more than fifteen days. A small majority showed a considerable quantity of peritoneal fluid which was more often simply turbid than thick. The fluid was without odor in three and foul in three. In three it was not noted.

Cases Yielding B. coli and a Streptococci without C. welchii—This group comprises twenty-six cases, twenty-two of which were due to appendicitis, three were classified as acute local peritonitis, fourteen as acute diffuse peritonitis and nine as peritoneal abscess (table 12). These patients as a group came to the hospital a trifle earlier than those in the preceding group, although fewer (two thirds) gave a typical history. The physical signs were much more marked than in the group yielding *B. coli* alone. Only a third had signs limited to one quadrant and in 50 per cent three or four quadrants were involved. Tenderness, rigidity and rebound tenderness were almost constant. Distention was present in three fourths of the cases. Blood counts, both total and differential, were a little lower. The patients were considered to be a little more seriously ill as a group on admission. Almost one third of these patients died and almost two thirds of them had serious complications. All but one patient among the survivors stayed in the hospital more than fifteen days. The peritoneal fluid was in general more profuse and thicker, and in four of the cases there was a frankly fecal odor. This group of cases is very similar to the one that follows except for the fact that it contains four more cases of acute diffuse peritonitis. On this account one would expect this group to show more pronounced symptoms. It must be remembered that in this group of cases besides *B. coli* and streptococci there were other organisms that may have played a rôle, but the same is true of the group that follows, so that the effect of this common factor may be discounted.

Cases Yielding B. coli, Streptococci and C. welchii—This group comprises twenty-two cases, thirteen of which were due to appendicitis. Three were classified as acute local peritonitis, ten as acute diffuse peritonitis and nine as peritoneal abscess (table 12). Almost three fourths of the patients came to the hospital after forty-eight hours. Only a little over half of the cases of appendicitis gave a typical history. Nausea, vomiting and fever were almost invariably present but chills were rare. On physical examination over half the patients were found

to have signs in four quadrants, although rigidity and rebound tenderness were less frequent than in the preceding group. Distention was a prominent feature. Total white cell counts were frequently low, although polymorphonuclear percentages were generally high. The patients were judged to be more severely ill than in either of the preceding groups. Almost half of them were placed in the severely ill class. About the same percentage of patients died, but those who died and those who survived had more serious complications, and all of those who survived stayed in the hospital over fifteen days. The peritoneal

TABLE 12—*Analysis of Certain Important Data in Nine Cases with B coli Alone, in Twenty-Six Cases with B Coli and Streptococcus without C welchii and in Twenty-Two Cases Yielding All Three Species*

	B coli Only		B coli and Streptococcus		B coli, Streptococcus and C welchii	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Total	9		26		22	
Typical appendicitis	6	75*	15	68	7	54*
Atypical appendicitis	2	25*	7	32*	6	46*
Quadrant 1	7	78*	9	35*	5	23
Quadrant 2	1	11	4	15*	6	27
Quadrant 3	0	0	4	15	0	0
Quadrant 4	1	11	9	35*	11	50*
White blood cells 16,000 +	5	72*	13	57*	10	48*
White blood cells 16,000 —	2	28*	10	43*	11	52*
Polymorphonuclears 80% +	5	72*	14	58*	13	68*
Polymorphonuclears 80% —	2	28*	10	42	6	32*
Mild	2	22	5	19	3	14
Moderate	6	67*	16	62*	9	41
Severe	1	11	5	19	10	46*
Recovered	9	100*	18	69*	16	73
Died	0	0	8	31*	6	27*
Fluid						
Little	4	44*	9	35	4	18
Much	5	56*	17	65*	18	82*
Turbid	6	67	15	58	9	43
Thick	3	33*	11	42*	12	57*
Odor						
None	0	0	14	70	4	20
Foul	3	50	2	10	7	35
Fecal	0	0	4	20	9	45

exudate was in general more profuse, and in a much larger percentage it was thick, while in 80 per cent it was either foul or frankly fecal.

Comment on the Data from the Standpoint of Symbiosis—Table 12 brings out some striking features. The first point is that all of the patients in the first group recovered from the single microbic infection but the mortality jumped to 31 per cent when the streptococcus and other organisms were present, with the exception of *C welchii*. In another group the mortality remained about the same when all three organisms were present. On the other hand, in all other categories an addition of *C welchii* led to an increase of symptoms, signs and sequelae and the peritoneal exudate was greater in quantity, showed more evidence of cellular activity and the odor became more offensive. There seems to be definite evidence from this study that the polymicrobic

infection is more severe than the monomicrobial, also that *C. welchii* may add to the severity of the illness, but there is no evidence of its preponderant or even important rôle in mortality

THE UNTOWARD RESULTS

We believe that much information can be gained in a study of this kind by a review of the untoward results either as a group or as individual cases

Fatal Cases—There were sixteen fatal cases. This group differs from the group in which recovery occurred in certain significant points brought out in table 13. The pathologic classification is of particular interest. Six of the seventy-six patients with appendicitis, or 8 per cent, died. No patients with appendicitis without perforation, whether acutely inflamed or gangrenous, succumbed. Death was limited to three of the eleven patients with perforated appendixes with acute diffuse peritonitis, two of the twelve in whom an abscess developed and one of the five patients with abscess whose appendix was not seen but was thought to have perforated. The mortality among all the other groups was higher, being 38 per cent in the cases of intestinal lesions, including the three cases of perforated ileum but only one of the five cases of perforated colon. The mortality in the cases in which the gallbladder had perforated was still higher, 50 per cent. In two of the fatal cases, the gallbladder had perforated spontaneously and in the third there had been leakage of bile either during or after operation. In the miscellaneous group one of eight patients died of a fulminating hemolytic streptococcic acute diffuse peritonitis.

Relation of Death to the Extent of the Process—If the fatal cases are grouped according to the extent of the process, it is seen that no patient with acute local peritonitis died, twelve, or 33 per cent, with acute diffuse peritonitis died and four, or 17 per cent, with abscess died. The time of admission into the hospital was no index of prognosis except so far as it was a determinant of the extent of the lesion.

Relation of Death to the Age of the Patient—Of the thirty-three patients less than 20 years of age, none died, and only three of thirty-three in the next two decades succumbed. Among patients of more advanced years, however, the mortality rate rose rapidly. There seems to be definite evidence that age was an important factor.

Relation of Death to the Symptoms and Signs on Admission—Fever was the only constant symptom in the fatal cases, while it was absent in ten of the ninety in which recovery occurred. The extent of the abdominal signs was not significant per se as an index. Each of the four fatal cases with abscess falls into a different group according to

TABLE 13—*Analysis of the Sixteen Fatal Cases Compared with the Ninety in Which Recovery Resulted*

Totals	Died, 16		Recovered, 90	
	Number	Per Cent	Number	Per Cent
Age				
0 to 20 years	0	0	34	100*
21 to 40 years	3	9	30	81
41 to 60 years	5	26	23	74
61 to 80 years	5	56*	4	44*
Diagnosis				
Acute appendicitis	0	0	37	100*
Perforated appendicitis, acute diffuse peritonitis	3	37	8	63*
Perforated appendicitis, abscess	2	17	10	83*
Perforated appendicitis (?), abscess	1	20	4	80
Gangrenous appendicitis	0	0	9	100
Volvulus, acute diffuse peritonitis	1	50	1	50
Perforated duodenum, acute diffuse peritonitis	1	50	1	50
Perforated ileum, acute diffuse peritonitis	3	100*	0	0
Perforated colon, acute diffuse peritonitis	1	33	2	67
Perforated gallbladder, acute diffuse peritonitis	3	100*	0	0
Hemolytic streptococcus, acute diffuse peritonitis	1	100*	0	0
Total acute local peritonitis	0	0*	47	100*
Total acute diffuse peritonitis	12	33	24	67*
Total abscess	4	17*	19	83*
Mild	0	0	32	100
Moderate	7	13	48	87
Severe	9	47	10	53
White blood cells 16,000 +	7	12	50	88
White blood cells 16,000 —	8	21	30	79
Polymorphonuclears 80% +	9	15	53	85
Polymorphonuclears 80% —	6	18	27	82
Sequelae 0	0	0	46	100
1 to 3	6	17	36	83
4 to 7	10	62	6	38
Pneumonia	10	67	5	33
Distention	10	38	16	62
Vomiting	8	50	8	50
Shock	6	86	1	14
Ileus	6	86	1	14
Retention of urine	6	46	7	54
Disruption of wound	1	50	1	50
Infection of wound	3	11	24	89
Fluid				
Little	3	6	48	94*
Much	13	24*	42	76
Clear	0	0	9	100*
Turbid	10	15*	58	85*
Thick	6	17*	29	83*
Odor				
?	3		27	
None	6	12*	44	88*
Foul	3	28*	10	72*
Fecal	4	31*	9	69*
Smear (forms seen)				
?	4		19	
0	3	9	31	91
1	1	8	11	92
2	4	20	16	80
3	4	24	13	76
Bacterial growth				
0 species	0	0	35	100
1 to 3 species	9	22	31	78
4 to 6 species	7	23	24	77
B coli	14	22	50	78
Green streptococcus	10	26	28	74
C welchii	7	25	21	75
B coli — green streptococcus	9	29	22	71
B coli ± nonhemolytic streptococcus	4	29	10	71
B coli — C welchii	6	27	16	73
B coli ±, streptococcus —, C welchii —	4	25	12	75
B coli ±, streptococcus —, C welchii ±	2	33	4	67

the number of quadrants involved. In the cases of acute diffuse peritonitis in which signs were found in one quadrant, two patients died and two recovered, in those with signs in two quadrants, one died and four recovered, in three quadrants, seven died and fifteen recovered. The severity of the cases was judged from the symptoms and signs on admission. Of the fatal cases, none was considered mild on the patient's admission, seven were in the moderately severe group, while nine were considered to be very serious. On the other hand, of those cases in which the patients survived, thirty-two were mild, forty-eight were moderate and ten severe. Thus 13 per cent in the moderate group and 47 per cent in the severe group were fatal. The blood counts are of interest, as in the other analyses. Of the thirty-eight cases with a total count below 15,000, eight, or 20 per cent, were fatal, while only seven of fifty-seven, or 12 per cent, with a count above 16,000 were fatal. Similarly, but without quite so much distinction a higher percentage of cases with a low polymorphonuclear count were fatal, (18 per cent) than those with a high count (13 per cent).

Relation of Death to the Postoperative Sequelae and Complications—Only one case without sequelae was fatal. Death came quickly within an hour of operation before complications could be noted. It was evidently due to the state of shock present before operation. Recovery occurred in forty-six other cases without sequelae. Of the patients with from one to three postoperative complications, five died and thirty-six recovered, a mortality of 12 per cent. Three of these died within forty-eight hours in a state of shock and two later of pneumonia. Of the sixteen patients having from four to seven postoperative complications, ten died 63 per cent. Ten of the patients who died had pneumonia, six had ileus, six had retention of urine and five suffered from shock. Nine of the fatal results came in the first six days, these were due primarily to the peritonitis. Five of the other seven patients lingered on from nine to twenty-one days and died primarily from fairly immediate complications of the peritonitis. One died in twenty-eight days and the other in eighty-five days from complications only remotely caused by the peritonitis.

The Relation of Death to the Growth of Organisms from the Peritoneal Exudate—Bacteria were cultivated from the peritoneal fluid in every fatal case. In nine, there were from one to three different species, in seven, from four to six different species. This contrasts strikingly with the patients who recovered. The peritoneal fluid from them yielded no growth in thirty-five, from one to three species in thirty-five and from four to seven species in twenty-four. In other words the mortality in thirty-five cases with no growth in the peritoneal fluid was zero. In forty cases with from one to three different species in the

peritoneal fluid and in thirty-one cases with from four to six species in the peritoneal fluid the mortality was 23 per cent. The identical mortality percentage in these last two groups makes one wonder whether or not there is some inhibition of bacterial activity when large numbers of species are present offsetting whatever effect increased numbers might have, or whether the minor species are simply inert and indifferent to the process. When one studies more specifically the bacterial species present, it is found that nonhemolytic *B. coli* was cultivated in fourteen, or 88 per cent, of the fatal cases, green streptococci in ten, or 63 per cent and *C. welchii* in seven, or 44 per cent. None of the other species was present in more than three, or 19 per cent of the fatal cases. All of these other species are apparently of secondary importance, except the hemolytic streptococcus, this organism is rare but of significance when it occurs, for it was found in only four cases in the series and two of these were fatal, one yielding the streptococcus in pure culture.

Comment on Fatal Cases—The table of fatal cases brings out strikingly several points. First, as to age incidence, whatever indeterminate factors play a part in the defense against peritonitis, youth has something that old age lacks. The nature and extent of the lesion had a profound effect in determining mortality. In the group of cases of appendicitis it is significant that death occurred only when there was a perforation with an escape of intestinal contents into the peritoneal cavity. Without perforation, even when numerous species of bacteria were found viable in the peritoneum, as for example in certain of the cases of acute appendicitis and gangrenous appendicitis, the patients recovered. The question arises as to whether death was the result of actual dosage, i. e., numbers of bacteria, of which we have no measure, or the presence of those intestinal fluids that are so irritating to the skin. Again, is it the digestive activity of these juices or simply their chemical reaction that is detrimental? Every patient with perforated ileum, and only one of the five patients with perforations of the large intestine, died. The ileal contents are alkaline, and the colonic contents are usually acid. What has the reaction to do with it?

It is of interest to note that none of the patients with acute local peritonitis died. One sixth of the cases of abscess would seem to be a higher proportion of fatalities than one would expect. However, when it is remembered that even when there is an abscess there is frequently a certain degree of diffuse peritonitis as well and that in opening an abscess the free peritoneal cavity is often entered, this may not seem too large.

That the damage is largely done before the patients come to the hospital is borne out by the estimation of severity in the fatal cases on their admission. Almost half of the patients who were severely ill on

admission died, only 13 per cent of those who were moderately ill died, and none of those who were mildly ill

The total white cell count was usually low with the percentage of polymorphonuclears relatively higher, which bears out the clinical experience in other suppurative lesions that turn out unfavorably

The sequelae are of particular interest. Pneumonia occurred in ten of the fatal cases. It was terminal, to be sure, in some of the cases, but in others it was a factor of importance. Excessive distention and excessive vomiting probably indicated the spread of the peritonitis and were present in practically every patient who survived more than a day or two. Shock, of course, was the chief immediate cause of death in the early fatalities, though in most cases it was due to the degree of the peritonitis

The bacteriology is our chief interest in these cases. The percentage of mortality increases rapidly when more than one organism is seen in smear or is grown out on culture. Only one patient died (the one with fulminating hemolytic streptococcic peritonitis) when a single species was present, and, surprising as it may seem, the mortality percentage when from four to six species were present was almost identical with that of the group with from one to three species. This has already been discussed. Again, the mortality for the three different groups containing the three common species is shown to be almost identical because of the overlapping and the fact that there was almost always more than one organism in the fatal cases. When these species are found together, either in pairs or all three together, the result is not appreciably altered. *B. coli* is so omnipresent that it is hard to rule out the importance of its presence, but we have no evidence that the presence of *C. welchii* increases the mortality or enhances the severity of the illness, or that either *C. welchii* or the green streptococcus is more effective than any other organism in enhancing the virulence of *B. coli*. Inasmuch as in our series of cases it is impossible to separate the bacteria from the succus entericus, we must not lose sight of the possible rôle that it plays in this malady. The high mortality of perforative lesions is shown graphically in chart 3.

The Factor of Resistance of the Individual in Mortality from Peritonitis—This is something that is very difficult, if not impossible, to measure. Perhaps the most significant indication of this is the age incidence in the fatal cases. This series, however, offers an interesting comparison of four cases strikingly similar in almost every respect namely age, diagnosis, extent of lesion, number and kind of bacteria found, severity of symptoms on admission, etc. Only one of these patients died. The one who died differs from the other three simply in the number of sequelae among which was a sudden cardiac failure

that was not explained as autopsy was refused. It is possible that his sequelae were the result of some unrecognized mistake in postoperative care, but he was in the ward and therefore subject to the care of the whole staff just as the other patients were. In another group of five similar cases, two died and three recovered without obvious explanation except the general resistance of the patient. One of these patients obviously had a factor of weakness in diseased kidneys. Our data do not give any definite information with regard to the resistance of the patients, but that it may be an important factor in the recovery from peritonitis must constantly be kept in mind.

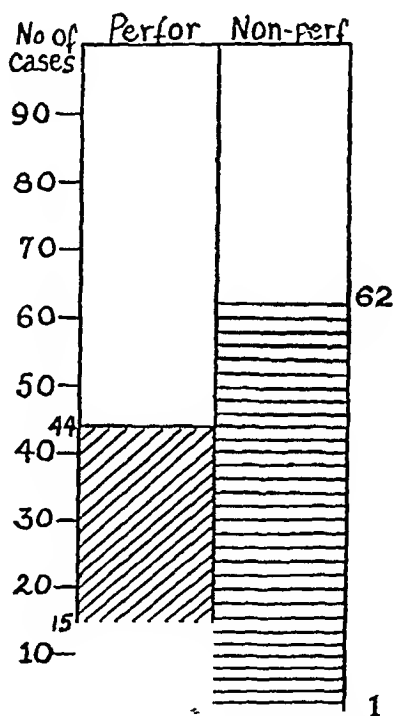


Chart 3—Incidence and mortality of perforative and nonperforative lesions. The shaded area indicates the number of cases in which recovery occurred, the solid area, the number of fatal cases.

GENERAL SUMMARY

We have studied intensively a small series of 106 cases of peritonitis and have made a bacteriologic examination of the peritoneal exudate taken at the time of operation. We have studied the conditions at this fixed point of time in the course of a pathologic process and have gone back to the beginning of the illness and on to the end in our clinical study to see what we could logically correlate in the clinical cinematograph with the condition at the moment of examination. It would be surprising if we could correlate everything, particularly with the innumerable factors at play both before and after but with certain

standard methods of procedure it was thought that it would be worth while to make the attempt at correlation and try to interpret our observations. We have studied the question from every angle that seemed to offer any hope of success. We hope that we have not attempted to get more out of our figures than they contain. With so many factors operating, it is only the outstanding features that are of any importance and only consistent results that cannot be explained away. In many respects our results tend to confirm the results of previous workers in this field who established facts that are such common knowledge that they have been the basis of our methods of treatment. In other respects, we are faced with surprising and unexpected results that do not fit our preconceived notions. We should like to emphasize the fact that we were prepared to find all of the known pathogenic spore-forming anaerobic organisms, having spent a considerable period studying their growth requirements before tackling this problem. By the use of blood agar plates and meat medium, *C. welchii* and the other spore-forming anaerobes are particularly easy to isolate and identify. Likewise, the *B. coli* group of organisms are easy to find. There is more difficulty in recovering the intestinal streptococci, because they vary so in artificial medium in their anaerobic requirements and their reaction to hemoglobin in blood agar plates.

Our studies seem to show fairly convincingly the following

- 1 The great majority of patients with peritonitis who come to a general hospital have lesions of the appendix. If the inflammation is limited in extent, the peritoneal exudate yields very few organisms on smear or culture.

- 2 If the appendix has not perforated, the disease is usually not fatal, whether the appendix is gangrenous or simply inflamed; the course is mild and the patients are able to return home in about two weeks.

- 3 If the appendix has perforated the inflammation is frequently extensive, the peritoneal exudate is profuse and yields great numbers of bacteria of several different species. The disease is frequently fatal; the course is stormy, and the patient who survives has to stay in the hospital about twice as long as if it had not perforated.

- 4 In gangrene of the appendix, we have no evidence from an examination of the peritoneal fluid that the spore-forming anaerobic bacteria, either pathogenic or nonpathogenic, are particularly active. When perforation of the appendix had taken place *C. welchii* was found in only twelve of thirty cases or 40 per cent, whereas *B. coli* was found in every instance. In nine cases of gangrene of the appendix without perforation *C. welchii* was not found once. Of the six fatal cases of perforative appendicitis *C. welchii* was found in only two or 33 per

cent, which is a lower proportion than its incidence in the whole group of cases of perforated appendix. When we included the cases of perforative appendicitis with the other gangrenous lesions of the appendix, we found that the anaerobes were present in practically the same proportion as in the nongangrenous group.

5 Perforative lesions of the small intestine promptly gave severe symptoms. There was usually extensive tenderness over the abdomen without distention. Total white blood cell counts were frequently low, with a relatively high percentage of polymorphonuclears. In the perforations of the upper intestinal tract, organisms were not usually seen on smear, and early cases yielded no growth. Perforations of the lower small intestinal tract were invariably fatal. The peritoneal exudate was usually profuse and turbid, many organisms were seen, and all yielded bacterial growth. In the nonperforative lesions of the small intestine, the severe symptoms were usually due to signs of intestinal obstruction with or without gangrene of the intestine. In these cases bacteria were usually found on culture in the peritoneal exudate, but smears indicated that they were not present in great numbers, and the patients usually recovered.

6 Perforative lesions of the large intestine in our series caused symptoms to develop more slowly, and in spite of the fact that they occurred in older people and more bacteria were found both in smear and in culture, including *C. welchii* which was invariably present, the large majority of these patients, four of five, recovered.

7 Perforative lesions of the gallbladder in our series were always fatal. The factor of bile irritation seems to be a potent one and several workers have reported that even if sterile, bile will cause a peritonitis which may be followed by the appearance of organisms in the peritoneal exudate.

8 Without respect to the cause of the peritonitis in three fifths of the patients coming to the hospital within twenty-four hours in our series, the lesion was local, the symptoms were mild, the peritoneal exudate was not profuse and organisms were rarely seen in smear or obtained in culture. Diffuse peritoneal inflammation was rarely found in cases with symptoms of less than twelve hours' duration, but usually in later cases. The cases with diffuse peritonitis were more severe, the peritoneal fluid was profuse, and usually many organisms were seen on smear and recovered in culture. Complications were frequent, and a third of the patients died. When abscesses had formed the history was usually of long duration although symptoms were moderately severe and there was much thick fluid containing many organisms both on smear and on culture. The mortality was just half that of the diffuse group. Of the three commonest organisms found namely *B. coli* the

green streptococcus and *C welchii*, there is a greater incidence in the diffuse than in the local, and a still greater incidence in the abscess, group. But in spite of the higher incidence, the mortality was less in the abscess group than in the diffuse group.

9 Smears of the peritoneal fluid made at the time of operation and compared with the culture seemed to be of real prognostic importance. When smears showed no organisms and cultures yielded no growth, or when fewer species appeared in culture than were seen on the smear, every patient recovered. These two observations warrant a favorable prognosis. When more kinds of organisms appeared on culture than were seen on the smear, there was an indication that certain organisms were potential of danger. More than one fifth of these patients died. When all of the forms seen on the smear grew out, the mortality was still higher, more than one-fourth perishing. The last two conditions warrant a guarded prognosis.

10 When cases of peritonitis were divided into groups according to the number of bacteria that appeared in the peritoneal exudate, it was found that thirty-five cases yielded no organisms, eleven yielded one, fourteen two, fifteen three, nineteen four, nine five, and three six species. In the great majority of cases yielding no growth, the disease was limited to the focus of infection. With viable organisms present, the majority of patients had acute diffuse peritonitis. With respect to certain symptoms and signs, there was a steady increase of severity corresponding to the number of species present. Other symptoms and signs were more severe in the group with from one to three species than in the group with from four to six. This suggests either that certain species found are inert or that there may be antagonistic effects of one bacterial species on another in the production of certain symptoms and antagonistic effects in the production of other symptoms.

11 There were three outstanding bacterial species in our series of peritoneal exudates. Nonhemolytic *B coli* was present in 87 per cent of the cases in which bacteria were found, green streptococci were present in 49 per cent and *C welchii* was present in 38 per cent. Altogether twenty-three different bacteriologic groups were recovered.

12 In our series, peritonitis was usually a polymicrobial disease. In only eleven of the seventy-one cases that yielded growth was a single species found. For that reason it was virtually impossible to evaluate the role played by each one. Any grouping to bring out a single factor was nullified by the presence of many common factors. The disease was worse in almost every respect when more than one organism was present than when there was a single organism. The importance of any of these species in our series seems to depend more on its prevalence than on its outstanding virulence. All of the evidence seems to show

that *C welchii* and the other spore-forming anaerobes as well as the anaerobic streptococci and diphtheroid bacilli do not appreciably increase the severity of the disease or increase the chance of a fatal outcome

13 There were no fatal cases in the acute local peritonitis group. A third of the cases of acute diffuse peritonitis were fatal. A sixth of the cases of abscess were fatal. All but one of the deaths occurred in cases of perforative lesions in which there was not only a bacterial but a chemical and a foreign body factor. These factors cannot be separated in clinical cases.

14 Every case of perforated ileum was fatal and only one of five in the group with perforated colon. Only one patient with a single infecting organism died, that organism was a hemolytic streptococcus.

15 The mortality percentage when from four to six species of organisms were present was almost identical with that of the group with from one to three species.

16 Although a third of our patients were less than 20 years of age, none of these patients died. In the next two decades only three of thirty died. After the age of 40 the mortality increased considerably with age.

17 Variations in outcome in patients of the same age who seemed to have practically identical pathologic and bacteriologic conditions at the time of operation indicate that the factor of individual resistance to peritoneal infection is an important one and must not be lost sight of.

CONCLUSIONS

1 It cannot be too strongly emphasized that the most important prophylactic treatment for peritonitis, as seen in a general surgical hospital, is early diagnosis and early operation in acute appendicitis.

2 A comparison of smear and culture with the pathologic condition at the time of operation gives a sound basis for prognosis.

3 In the great majority of cases yielding bacteria in our series, there was a polymicrobial infection. In any specific prophylactic or active treatment for bacterial peritonitis one must take into consideration the symbiosis of the commonest organisms found in the peritoneal exudate, namely *B coli*, the green streptococcus and *C welchii*.

4 The mortality in perforative cases was so much greater than in the nonperforative cases in our series that the rôle of the intestinal juices must not be forgotten.

5 The results of this study lay the ground work and point the way to some specific experimental studies, of which may be mentioned (a) vaccine and serum prophylactic and active treatment (b) the bacteriostatic effect of peritoneal fluids (c) the neutralization of digestive ferments and (d) the synergisms and antagonisms of certain bacteria.

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OXYGEN THERAPY

INSUFFLATION INTO ORAL PHARYNX^{*}

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Dyspnea, cyanosis and other signs and symptoms are, of course, evidence of want of oxygen and are usually abated in a patient who is benefited by oxygen therapy. Clinical experience, however, has led us to believe that reduction of the pulse rate is by far the most reliable single guide by which to judge benefit, or failure of benefit, from the administration of oxygen-rich atmosphere. It is therefore desirable that when oxygen therapy is instituted, as high a concentration as is mechanically available should be first begun. Meanwhile a careful charting of the pulse rate should be made at least every fifteen minutes. With high concentrations, approaching 100 per cent, the pulse rate will probably be reduced during the first few hours. If such an effect is not secured, careful adjustment of the method of administration having been made to assure the operator that an extremely high percentage of oxygen has been displayed at the glottis, effort beyond a few hours is futile, and the attempt should be abandoned. If, however, a definite reduction in pulse rate does take place, reduction of the oxygen flow may then be made until such a point is reached that the maximum reduction of pulse rate is still maintained. This should be chosen as the optimum concentration for that patient, and the interval between pulse rate readings can be lengthened to one hour. At the slightest rise in pulse rate or the return of dyspnea the oxygen concentration should be increased until the maximum clinical effect is again obtained.

When the clinical progress has reached such a point that the necessity for excess oxygen in the inspired atmosphere appears to be no longer indicated fifteen minute readings of the pulse rate are again instituted, accompanied by gradual small reductions in the concentration of oxygen. Whenever the pulse rate tends to increase, the concentration of oxygen must again be raised. So over a period of from twenty-four to forty-eight hours in the usual case sometimes more rapidly oxygen therapy should be gradually discontinued. The physician should at all times bear in mind that the change in atmospheric environment during

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the interruption of oxygen therapy is not unlike that experienced by a person in traveling from sea level to mountain peak. The circulatory muscle of a person whose heart reserve is adequate in ordinary life has occasionally been greatly embarrassed by such a change. Nothing short of an elevator or airplane ascent could simulate the rapidity with which reduction in percentage of oxygen takes place during sudden withdrawal of oxygen therapy. In certain instances extremely gradual reduction to normal atmospheric conditions has been found necessary.

Administration of excess oxygen by means of a catheter passed through the nares is one of the simplest and most generally available methods. As to the efficiency of this technic, opinions expressed in the literature are at extreme variance. Evans¹ recently compared the nasal catheter to the old-fashioned funnel suspended over the patient's face and attached to a small oxygen tank and wash bottle through which 200 or 300 cc. of oxygen a minute were allowed to flow. McCleod and others have, of course, long since called attention to the absolute inefficiency of the funnel method. On the other hand, Barach² recently showed that inspired oxygen can be raised to above 35 per cent by allowing 5 liters of oxygen to flow through a nasal catheter. A more or less superficial experience with oxygen therapy by this means over a period of ten years, together with observations in the routine administration of several anesthetic agents, mixed with oxygen in various percentages, by pharyngeal insufflation, led to the impression that much higher percentages could be reached than those reported by Barach.

In administering anesthetic gases and vapors by pharyngeal insufflation, the position of the tip of the catheter in the pharynx has proved important. Efficient anesthesia cannot be maintained with minimum quantities when the delivery is in the nasopharynx. Even with a maximum flow of gases, when the tip of the catheter is in the nasopharynx, the gases flow in one nostril and out the other or around the catheter rather than pass the soft palate into the oral pharynx and to the glottis. To maintain efficient anesthesia by means of pharyngeal insufflation, the catheter tip must be inserted well into the oral pharynx, the nearer the glottis the better. Similar physical principles are involved in the pharyngeal insufflation of oxygen. The therapeutic use of pharyngeal insufflation, however, often necessitates passing the catheter through the nostril of a semiconscious or noncooperative patient. The tip of the catheter must lie in an oral pharynx in possession of normal reflexes. Great care and sometimes considerable diplomacy is necessary in successfully placing and fixing the catheter in proper position.

1 Evans, John. *Am Med* **24** 211, 1929.

2 Barach, A. L. *Administration of Oxygen by Nasal Catheter*, *J. A. M. A.* **93** 1550 (Nov. 16) 1929.

In order to determine whether high concentrations of oxygen could be maintained at the glottis of conscious patients by means of pharyngeal insufflation, the following experiments were performed

EXPERIMENTS

Rubber urethral catheters no 8 or 10 F were used. Each catheter was perforated with four extra holes in the terminal half inch as suggested by Barach.² Multiple openings prevent the possibility of a constant stream of oxygen striking

Oral Pharyngeal Insufflation of Oxygen, Showing Quantity of Oxygen Flowing and Gas Analyses of Samples Taken Near Glottis

Oxygen, Cc per Minute	Inspiration		Expiration		Comment
	Oxygen	Carbon Dioxide	Oxygen	Carbon Dioxide	
1,500	26.0	0.2	23.0	4.2	Catheters $4\frac{1}{2}$ to $5\frac{1}{2}$ inches from exterior nares
2,200 1,800	29.8		25.4	4.2	Nasal breathing
2,200 1,800	27.5	0.5	25.0	3.8	Oral breathing
2,800 2,720			34.6	4.0	Oral and nasal breathing
4,200 3,100			36.1	4.1	Oral and nasal breathing
4,200 4,120			37.8	4.0	Oral and nasal breathing
4,800	45.7				Oral and nasal breathing
5,200 4,400	50.0	0.4	41.0	4.0	Oral and nasal breathing
4,800	54.7	0.7			Nasal breathing
6,180	39.0		43.0	4.3	Catheters withdrawn slightly
8,400	53.0		53.0	4.6	Catheters withdrawn slightly
6,000			72.4	2.6	Catheter beyond 5 inches, mouth closed, gas swallowed
6,000			70.0	2.6	Same as preceding observations
6,000			71.1	2.6	Catheter $4\frac{1}{2}$ to 5 inches, from exterior nares, nasal breathing, no gas swallowed
6,000			71.6	2.2	Same as preceding observa- tions, oral breathing
10,000	74.2	0.2			Catheter $4\frac{1}{2}$ to 5 inches from exterior nares mouth closed

one spot on the pharyngeal mucosa and thus annoying the patient and irritating the membrane. The likelihood of blocking the one opening when negative pressure is applied in taking samples from the pharynx is also obviated. The sample catheter was inserted through the nostril and down the posterior wall of the pharynx to a point opposite the glottis or nearly so. The taking of tracheal samples seemed unjustifiable in conscious patients. The delivery catheter was inserted in the other nostril with oxygen flowing. It was advanced slowly down the oral pharynx until the subject found that a bolus of oxygen was swallowed during the act of deglutition. (A cooperative subject easily determines this point. The fact that gas is swallowed during deglutition is, however, very evident to the observer.) The catheter was then slightly withdrawn until no gas was swallowed during deglutition. This point had been previously found to be the optimum position to secure good clinical results in oxygen therapy.

With "sample" and "delivery" catheters placed as described, a known volume of oxygen per minute was allowed to run through the delivery catheter, and samples were taken by means of negative pressure applied for short periods during each respiratory cycle, from two to four minutes being consumed in taking each sample

The resulting analyses of these samples with the number of cubic centimeters of oxygen per minute flowing through the delivery catheter are set forth in the accompanying table. Notes are added in some cases, as to the time samples were taken in the respiratory cycle, and whether the mouth was closed or open

Certain facts are evident from these experiments

1 The possibility of administering oxygen in concentrations in excess of 70 per cent by means of a catheter placed in the oral pharynx of a conscious patient is established. A flow of from 7 to 8 liters per minute is capable of maintaining a percentage well in excess of 50 at the glottis

2 Whether the mouth is open or closed has much less effect on the concentration of oxygen at the glottis than does the position of the catheter and the rate of flow of the oxygen

3 The position of the delivery tip of the catheter is very important. Careful fixation of the catheter with adhesive strips is essential to the comfort of the patient. When properly placed and properly fixed almost no sensation is experienced by the subject other than one of comfort and ease in breathing. The position of the catheter does not seriously interfere with swallowing of food or with speech

4 The catheter, once ideally placed, should be marked at the exterior nares in order properly to place a fresh catheter at twelve hour intervals in the alternate nostril. The proper distance of the catheter tip from the exterior nares, in the subjects used for these experiments, varied between $4\frac{1}{2}$ and $5\frac{1}{2}$ inches (11.4 and 13.9 cm). Viewed through the mouth this position was usually about level with the tip of the uvula as it hung quiescent during nasal breathing

5 Small urethral catheters of a size not to exceed 10 French are ideal for this purpose, but, as suggested by Barach, they should carry extra holes punched in the terminal half inch

COMPARATIVE ADVANTAGES AND DISADVANTAGES

Consumption of Oxygen—By means of the pharyngeal catheter properly placed, concentrations of oxygen at the glottis in excess of 50 per cent can be maintained with a flow not exceeding 7 liters. Reports from clinics (Columbia Hospital Milwaukee, and the Mayo Clinic Rochester, Minn.) using oxygen chambers estimate the volume of oxygen used as from 7 to 8 liters per minute to maintain concentrations between

50 and 60 per cent Roth³ reported that a flow of from 5 to 6 liters per minute will maintain from 50 to 60 per cent concentration in the oxygen therapy tent, provided the tent flaps are kept carefully tucked in and no leaks are permitted. Evans¹ reported the consumption of oxygen to be as great when a face mask is used. By the use of soda lime absorption of carbon dioxide and a closed inhaler and breathing bag we have been able to administer pure oxygen atmosphere to a patient at forty-five minute intervals over a fifty-four hour period with an average consumption of 620 cc per minute. Such a method however we believe to be applicable only to patients with chronic conditions who are not annoyed by a tightly fitting face mask.

Cost of Equipment—The equipment necessary for the use of catheters is cheap and easily procured wherever compressed gases are used. Tanks and pressure-reducing gages can often be rented for short periods. The original cost of chambers for oxygen therapy has been estimated at from \$3,000 to \$5,000 per bed. Tents require less large original investments.

Supervision—The catheter technic requires great care as to proper fixation of the tube and as to maintaining a sufficient flow of oxygen. Nursing care is not embarrassed in any way. Chambers require careful mechanical maintenance of carbon dioxide removal and moisture regulation. Nursing care is ideally easy, but expensive. In the use of tents extreme care is necessary to maintain the concentration of oxygen in the face of the necessity for raising tent flaps during feeding, expectoration, etc.

In conclusion, evidence is presented to show that, with proper care in placing catheters in the oral pharynx barely short of the point at which swallowing of gas occurs during deglutition, ample concentrations of oxygen can be maintained in the inspired atmosphere to accomplish satisfactory clinical results.

3 Roth, Paul. J. Lab. & Clin. Med. 12: 388, 1928.

THE RÔLE OF TOXIN OF BACILLUS WELCHII IN THE TOXEMIA OF ACUTE INTESTINAL OBSTRUCTION

AN EXPERIMENTAL STUDY¹

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The presence of bacteria in the lumen of an obstructed bowel is necessary for the production of the lethal substances that produce the toxemia of acute intestinal obstruction. This bacterial origin of the toxin in the content of the obstructed bowel is being universally accepted. It has been amply proved by the investigations of Murphy and Vincent,¹ Murphy and Brooks,² Brooks, Schumacher and Wattenberg,³ Dragstedt, Moorhead and Burcky,⁴ Dragstedt and Moorhead,⁵ and Dragstedt, Dragstedt, McClintock and Chase.⁶

The exact nature of the toxins formed in the obstructed bowel is not known. In 1918 Dragstedt, Dragstedt and Chase⁷ concluded that no immune bodies are produced following the repeated injection of fluid from obstructed loops of bowel into the veins of rabbits. A further conclusion from their study was that the toxic properties of this fluid are probably not of protein nature. Before these workers injected the

¹ Submitted for publication, April 14, 1930

² From the Department of Surgery, Indiana University School of Medicine

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1 Murphy, F T, and Vincent, Beth. An Experimental Study on the Cause of Death in Acute Intestinal Obstruction, Boston M & S J **155** 684, 1911

2 Murphy, F T, and Brooks, B. Intestinal Obstruction. An Experimental Study of the Causes of Symptoms and Death, Arch Int Med **15** 392 (March) 1915

3 Brooks, B, Schumacher, H W, and Wattenberg, J E. Intestinal Obstruction. An Experimental Study, Ann Surg **67** 210, 1918

4 Dragstedt, L R, Moorhead, J J, and Burcky, F W. Intestinal Obstruction. I. An Experimental Study of the Intoxication in Closed Intestinal Loops, J Exper Med **25** 421, 1917

5 Dragstedt, Carl A, and Moorhead, J J. Immunity in Intestinal Obstruction, J Exper Med **27** 359, 1918

6 Dragstedt, L R, Dragstedt, Carl A, McClintock, J T, and Chase, C S. Intestinal Obstruction. II. A Study of the Factors Involved in the Production and Absorption of Toxic Materials from the Intestine, J Exper Med **30** 109, 1919

7 Dragstedt, Carl A, Dragstedt, L R, and Chase, C S. The Antigenic Property of Closed Intestinal Loop Fluid, Am J Physiol **46** 366, 1918

toxic fluid into the rabbits, they heated it to 70 C on a water bath for an hour. An interest in heat-labile toxins of fluid in the obstructed bowel has been stimulated by researches conducted since these communications were made.

Williams,⁸ a British surgeon, advanced the hypothesis that the toxin of *Bacillus welchii* is the toxic agent in acute intestinal obstruction. Some strains of this organism produce a powerful myotoxin which is heat-labile. In support of his theory, Williams pointed to the similarity between the clinical pictures of intestinal obstruction and of *B. welchii* infection. He found the organisms in the vomitus from patients with obstruction, demonstrated the presence of the toxin in the filtrate of the content of the obstructed bowel by animal inoculation and lowered the mortality rate clinically by giving *B. welchii* antitoxin to groups of patients with intestinal obstruction and peritonitis.

Bower and Clark,⁹ and Morton and Stabins¹⁰ submitted clinical and experimental evidence of the therapeutic value of *B. welchii* antitoxin in acute intestinal obstruction and peritonitis. Stabins and Kennedy¹¹ demonstrated that a rapid growth of *B. welchii* organisms occurred soon in isolated loops of bowel from which they failed to culture such organisms before the obstruction was produced. McIver, White and Lawson¹² found from cultural studies of the bacterial flora of the obstructed loops of bowel in cats that the number of *B. welchii* organisms was always so increased that there was no doubt that this was the predominant organism.

McClintock and Hines¹³ studied the occurrence of heat-labile toxins in closed intestinal loops. They injected the Berkefeld filtrate of the loop fluid intraperitoneally, using two series of guinea-pigs. In one series the unheated filtrate was used, in the other, an equivalent amount of filtrate heated for one hour to 65 C was injected into the peritoneal cavity. In six animals that received the unheated fluid, death occurred in from twelve to forty-eight hours. In six control animals the heated fluid failed to cause marked toxemia or death. They failed to demon-

8 Williams, B. W. The Importance of Toxemia Due to Anaerobic Organisms in Intestinal Obstruction and Peritonitis, *Brit J Surg* **14** 295, 1926.

9 Bower, J. O., and Clark, J. *Bacillus Welchii* Antitoxin. Its Therapeutic Value, *Am J M Sc* **176** 97, 1928.

10 Morton, J. J., and Stabins, S. J. Experimental Studies on the Relation of *Bacillus Welchii* Antitoxin to the Toxemia of Acute Intestinal Obstruction, *Arch Surg* **17** 860 (Nov) 1928.

11 Stabins, S. J., and Kennedy, J. A. The Occurrence of *Bacillus Welchii* in Experimental High Intestinal Obstruction, *Arch Surg* **18** 753 (Feb) 1929.

12 McIver, M. A., White, J. C., and Lawson, G. M. The Role of the *Bacillus Welchii* in Acute Intestinal Obstruction, *Ann Surg* **89** 647, 1929.

13 McClintock, J. T., and Hines, H. H. The Occurrence of Heat-Labile Toxins in Closed Intestinal Loops, *Proc Soc Exper Biol & Med* **26** 654, 1929.

strate the presence of the toxin of *B welchii* in the fluid of the obstructed loops

Scholefield¹⁴ confirmed the observations of Sugito¹⁵ that blood withdrawn during the last moments of life from radicles of the portal vein draining an obstructed loop of the intestine of the dog is toxic for mice. While the serum was separating, it was kept at a low temperature and then was injected into the peritoneal cavity of mice. It killed them in from three to fourteen hours. The serum from normal dogs was not toxic for mice when given in similar quantities.

Prati¹⁶ used the supernatant fluid from a centrifugated extract of feces from both the normal and the occluded bowel of dogs. He injected this subcutaneously into guinea-pigs, using a control series protected by *B welchii* antitoxin. He found that *B welchii* antitoxin reduced materially the toxicity of these extracts. When the extract of the content of the occluded bowel was given the animal lived for an average of eight hours. When given the extract to which *B welchii* antitoxin was added, the animals lived for an average of twenty-two hours.

The exotoxin produced by *B welchii* contains both a myotoxin and a hemolysin, as shown by Bull and Pritchett¹⁷ and by Henry¹⁸. This exotoxin is weakened when it is exposed to the air, and it is destroyed by heating to 70 C. for thirty minutes. Animals subjected to sublethal doses of the exotoxin produce an antitoxin that is monovalent. The antitoxin neutralizes this toxin in multiple proportions and the hemolysin as well as the myotoxin is neutralized.

The myotoxin, strongest in fresh cultures from twelve to twenty-four hours after inoculation, may disappear on the second or third day.

14 Scholefield, B. G. Acute Intestinal Obstruction. Experimental Evidence of the Absorption of Toxin from the Obstructed Bowel, with a Critical Review of Various Methods of Treatment, *Guy's Hosp Rep* **77** 160, 1927.

15 Sugito, Su. Ueber die Todesursache bei Ileus, *Mitt a d med Fakult d k Univ Kyushu Fukuoka* **9** 229, 1924, quoted by Scholefield (footnote 14).

16 Prati, Mario. The Presence of Perfringens Toxin in the Contents of the Normal and Occluded Intestine, *Boll d Ist sieroterap milanese* **8** 165 (March) 1929.

17 Bull, Carroll, G., and Pritchett, Ida, W. The Toxin and Antitoxin of and Protective Inoculation Against *Bacillus Welchii*, *J Exper Med* **26** 119, 1917, The Prophylactic and Therapeutic Properties of the Antitoxin for *Bacillus Welchii*, *ibid* **26** 603, 1917, Identity of the Toxins of Different Strains of *Bacillus Welchii* and Factors Influencing Their Production in Vitro, *ibid* **26** 867, 1917.

18 Henry, Herbert. On *B Welchii* Hemotoxin and Its Neutralization with Antitoxin, *J Path & Bact* **25** 1, 1922, The Precipitation of *B Welchii* Toxin, *ibid* **23** 273, 1919, 1920, On the Composition of *B Welchii* Toxin, *ibid* **26** 497, 1926.

(Henry¹⁹) Reed and Spence,²⁰ and Barach and Draper²¹ demonstrated an antihemolysin in rabbits three weeks after the injection of small amounts of the toxin of *B welchii* its maximum in seven weeks and persistence for a year Henry¹⁹ reported that the amount of antitoxin necessary to protect mice against the myotoxin is much less than that necessary to neutralize the hemolysin

EXPERIMENTAL STUDIES

In these studies experiments were made to secure evidences directly as well as indirectly of the absorption of the toxin of *B welchii* from closed intestinal loops produced in dogs

1 B Welchii Antitoxin in Dogs with Isolated Intestinal Loops—In thirty-five strong, medium-sized, short-haired dogs a loop of jejunum was isolated and an end-to-end anastomosis of the bowel was made Each animal was given 1 grain (0.066 Gm) of morphine sulphate subcutaneously and ether anesthesia The jejunum was transected 10 cm below the ligament of Treitz and loops from 15 to 35 cm long were isolated The Parker-Kerr²² technic of end-to-end anastomosis was used to establish the continuity of the intestine The ends of the isolated loop were closed by the Parker-Kerr technic, care being used to turn in no more of the bowel end than was absolutely necessary Many of the animals, at the beginning of the study received by hypodermoclysis 0.5 liter of normal physiologic solution of sodium chloride This was not continued for it was found that they recovered well from the operation without it All of the animals were given as much food and water as they cared to take

Twenty of the animals were given 5 cc of concentrated *B welchii* antitoxin daily from the day of the operation until their death The only exception to this was due to a temporary shortage of the antitoxin when two or three animals missed their dosage for a day or two The antitoxin was given subcutaneously and the injections were begun on the day of operation It was supplied by the Mulford Company and was standardized so that 1 cc would neutralize 5,000 minimal lethal doses of the toxin of *B welchii*

The fifteen animals in the second series were treated exactly as the animals of the first series, except that they received no antitoxin Three of these animals, one of the protected series (no. 65) and two of the control series (nos. 38 and 64), recovered well from the operations, and ate heartily but became progressively emaciated Finally anorexia developed When it seemed that the animals would die soon, the abdomen was reopened and the isolated loop was removed The conditions in these three animals were most interesting and are considered in section 4 of this paper The loops were resected on the twenty-sixth day, the forty-third day and the sixteenth day respectively after operation In striking

19 Henry (footnote 18, third reference)

20 Reed, G. B., and Spence, M. Duration of Immunity to Bacillus Welchii Toxin (in Rabbits), *J. Infect. Dis.* **41**: 428, 1927

21 Barach, A. L., and Draper, G. Studies in Experimental Anemia. Immunologic Study of Relation Between Pernicious Anemia and Anemia Due to Welch Bacillus Toxin, *J. Clin. Investigation* **4**: 539, 1927

22 Kerr, Harry H. The Development of Intestinal Surgery, *J. A. M. A.* **81**: 641 (Aug. 25) 1923

an average length of life after operation for comparison, the day the loop was resected was considered as the day of death

Postmortem examinations of all the animals were made to determine the cause of death. In five of the dogs receiving antitoxin a simple obstruction was found. In four animals this was caused by invaginating too much bowel wall when the end-to-end anastomosis was performed in the first group of operations, and was due to inexperience with the type of technic used. The simple obstruction in the fifth dog was due to a hairy bezoar. These dogs lived for 10, 10, 14, 8 and 24 days. At postmortem examination in none of these was the loop ruptured and there were evidences in each of dehydration and starvation. The mucosa within the loop was intact and there was no necrosis of its wall. In two of them the loop was extremely flabby and its content quite pasty, owing to absorption of fluid

TABLE 1—*Length of Life of the Animals After Operation*

Series A Animals Receiving B Welch Antitoxin (20 Dogs)*					
Number of Animals	Condition	Duration of Life, Days	Average Duration of Life of Whole Group, Days	Average Duration of Life of Animals With Toxemia and Peritonitis, Days	Average Duration of Life of Toxemic Animals, Days
1	†Toxemia and resected loop	26			
4	Toxemia and unruptured loop	2, 2, 3, 1			
10	Toxemia and ruptured loop	2 5, 4, 2, 10, 8, 4, 2, 3, 3, 3			
5	Toxemia and simple obstruction	8, 10, 10, 14, 24			
			7 0	3 5	2 0
Series B Control Animals (15 Dogs)					
2	†Toxemia and resected loop	43, 16			
5	Toxemia and unruptured loop	5, 2, 2, 5, 3			
8	Toxemia and ruptured loop	1 25, 2, 4 5, 1 5, 4, 5, 3, 6			
			6 8	3 4	3 4

* No beneficial effects from the administration of B Welch antitoxin were observed.

† The duration of life of these animals was taken up to the time of the resection of the loop.

Four of the twenty animals that received antitoxin died. Autopsy disclosed an unruptured loop enormously distended, discolored and with a necrotic mucosa but no gross evidence of peritonitis. In each dog there was a serosanguineous transudate free in the peritoneal cavity. The average length of life of these animals was two days.

The characteristic features of the conditions found at autopsy in the animals with ruptured loops were those found by van Beuren²³. The loops had been enormously distended. They were discolored with purple to black gangrenous patches and with perforations opposite the mesentery. A virulent peritonitis had occurred in some. In others the animals were apparently overwhelmed by rapid absorption of toxins from the liberated loop fluid before peritonitis developed.

The average length of life of the "protected" series was 7 days and that of the control series 6.8 days. Removing from consideration the animals from which the loop was resected and those having simple obstruction, the average length

²³ Van Beuren, F. T. The Mechanism of Intestinal Perforation Due to Distention, *Ann Surg* 83: 69, 1926.

of life of the fourteen protected animals was 35 days and that of the thirteen control animals 34 days

Five of the control animals died with an unruptured loop and with evidence of acute toxemia. The average length of life of these animals was 34 days, 14 days longer than the average of the same group of the series receiving *B welchii* antitoxin

2 The Immunization of Dogs by *B Welchii* Toxin—A series of eight short-haired dogs of uniform size were inoculated with the toxin of *B welchii*. A toxin, made by Dr H W Cromwell, from a virulent strain of *B welchii*, was supplied by the Swan-Myers Company. The minimal lethal dose of each lot of toxin was determined by intramuscular injection into pigeons. The animals were given six injections of toxin made at weekly intervals. The first injection was made intramuscularly and consisted of a sufficient quantity of the Berkefeld filtrate of a broth culture to contain 5 minimal lethal doses. Following two or three injections there was a marked local reaction. After the second dose of the filtrate further immunization was carried out by intravenous injections of the unfiltered cultures. The dosage was gradually increased until a final dose of 12 minimal lethal doses was given. Some of the culture occasionally escaped into the areolar tissue along the vein, but no local reaction was produced. One of the eight animals died from distemper, and another following a fight, a third was not used because it was ill.

Seven weeks after the first inoculation of *B welchii* toxin was made, five of the eight animals were bled and their serum was used in an attempt to protect pigeons against lethal doses of *B welchii* toxin as well as in tests for hemolysis.

The serum was kept at icebox temperature until the tests were made. For the inhibition of hemolysis tests an eighteen hour broth culture of *B welchii* with a pH of 7 was centrifugated at high speed for an hour. The serum from the dogs was mixed with the supernatant fluid from the centrifugated broth culture and incubated for one hour on the water bath at 56 C. A 5 per cent suspension of rabbit red blood cells, washed with Ringer's fluid was added to the serum and toxin, and the serum-toxin mixture was again incubated for an hour. Adequate controls were employed. Two of the five animals gave no evidence of anti-hemolysin in their serum. The serum from two dogs gave complete protection, and one gave partial protection, against hemolysis (table 2).

The serum from the two dogs giving strong protection against hemolysis also protected pigeons for forty-eight hours or longer against 23 and 24 minimal lethal doses of *B welchii* toxin, respectively. The serum containing moderate quantities of antihemolysin protected a pigeon for more than forty-eight hours against only 24 minimal lethal doses. Serum from the animals that contained no antihemolysin did not protect pigeons against 1 minimal lethal dose of the toxin.

Isolated loops, from 30 to 45 cm long, were produced in these three animals in the same manner as in the animals reported in section 1. One animal died after forty-eight hours with a ruptured loop and general peritonitis, and another after nine days with the same conditions. The serum of this animal gave the least protection to a pigeon. The third animal died from absorption of toxin from the isolated loop after fourteen days. Postmortem examination of the third animal revealed a distended, intact, isolated loop with a hypertrophied wall. There was a serosanguineous transudate free in the abdominal cavity.

3 Loop Toxin and *B Welchii* Toxin in the Veins of Dogs—From 5 to 8 cc of fluid from the isolated loops of two dogs were injected into the veins of three others. For two of these animals the toxic fluid from the loop of dog 38 of

section 1 was used. For one of these, a medium-sized dog, an equal quantity of the concentrated *B welchii* antitoxin was mixed with 75 cc of the loop fluid, allowed to stand a few minutes and then injected. The typical clinical and pathologic complex was observed in each of these dogs. The dog receiving the combined doses of *B welchii* antitoxin and toxic loop fluid responded more quickly, clinically, to the intoxication than did the other two. From within a moment or two to within half an hour after injection the onset of these symptoms occurred in the three animals. There was dilation of the pupils, involuntary urination, marked retching and vomiting, diarrhea—extremely bloody in one case—hyperpnea and tremors and weakness of the posterior extremities. Coma intervened before death. The animals died in from one and a half to twelve hours after the injection. These symptoms were enumerated by Cooper²⁴ who thoroughly reviewed the recent literature dealing with intestinal obstruction.

At postmortem examination the lungs appeared collapsed and grossly normal. There was no evidence of hemolysis-staining of the lining of the heart or of the intima lining the larger blood vessels. About two thirds of the lining of the lower part of the duodenum, jejunum and ileum was blotched with petechial hemorrhages. The bowel content everywhere was red from bleeding.

TABLE 2—Data Pertaining to the Immunized Animals

Dog	Condition	Duration of Life Days	Inhibition of Hemolysis on Titration of Serum	Extent of Protection of Pigeons by Serum, M L D
70	Toxemia and peritonitis	2	Complete	1 cc protects for 23 M L D
71	Toxemia	14	Complete	1 cc protects for 24 M L D
83	Toxemia and peritonitis	9	Partial	1 cc protects for 24 M L D

* Complete and partial inhibition of hemolysis in the blood serum of these animals indicates the presence of some antihemolytic substance or substances. The protection of the pigeons against 1 M L D or more of the toxin indicates the presence of immune bodies against the myotoxin.

Sufficient of the broth culture of *B welchii* (60 cc) to contain 300 fatal doses for a pigeon was injected into the vein of another dog. A slight reaction occurred from this, such as a moderate diarrhea and retching. No such marked clinical symptoms occurred with the use of this toxin as when a very much smaller quantity of loop fluid was given. This difference was striking. The death of the animal occurred in twelve hours. On postmortem examination there were small areas of petechial hemorrhages of the lining of the lower part of the duodenum and of the jejunum and ileum. The bowel content was greenish brown. The blood in the cavities of the heart and large vessels was fluid, and the linings of these cavities were wine-colored from staining by hemolysed blood.

If the toxins of *B welchii* were the lethal bodies of the loop fluid the *B welchii* antitoxin should have neutralized them and delayed the response of the animal to the effects of the loop fluid. The *B welchii* antitoxin gave no protection whatever. Dogs vary greatly in their response to the intravenous injection of fluid from occluded loops, some requiring large doses before death occurs. In those reported here, however, a much smaller quantity of the loop fluid than of the broth culture was required for fatal effects.

4 *Effects of the Continued Absorption of Isolated Loop Fluid*—This report has to do with the three animals mentioned in section I from which the isolated

²⁴ Cooper H S F. The Cause of Death in High Obstruction. Arch Surg 17 918 (Dec) 1928.

loops were removed before death occurred. One of them (no 65) (table 3) was of the series that received 5 cc of *B welchii* antitoxin subcutaneously for eight days until the supply became exhausted temporarily. Its regular use was discontinued thereafter, and the animal had received no antitoxin for twelve days before the resection of the loop. There was progressive emaciation in spite of a heavy intake of food. For four or five days before the resection of the loop anorexia developed. This became so extreme that the dog could not be induced to take any food. The emaciation was extremely marked. On the twenty-sixth day after the isolation of the loop the abdomen was again entered under light ether anesthesia and the loop resected. Within a month after the resection of the loop the animal became well nourished again.

The length of the loop had increased from 35 to 78 cm, and its circumference was 12 cm. It contained 650 cc of grayish-green fluid. The mucosa of the loop was everywhere intact, and the fibrous and muscle tissue of the wall of the bowel was grossly thickened. The lumina of the blood vessels, particularly the veins, in the mesentery of the loop were from two to three times larger than they were when the loop was isolated.

The death of a pigeon occurred within eighteen hours after 10 mg of the fluid from the loop was injected into the breast muscles. A strip of the muscle was removed aseptically and cultured anaerobically. There was a growth of gram-positive rods which produced a storm clot in milk mediums and which had the morphologic characteristics of *B welchii*. The serum of blood removed from dog 65 at the time of the resection of the loop was kept at icebox temperature and was used in the attempt to protect pigeons from the lethal effects of the toxin of *B welchii*. One cubic centimeter of the serum gave no protection for 1 minimal lethal dose. When one month had elapsed after the resection of the loop the animal was again bled and the blood serum was studied to see if it contained an antihemolysin. The method used was that described by Henry²⁵ for the neutralization of the toxin by the serum. Complete hemolysis occurred and there was no neutralization of the toxin by the blood serum.

Emaciation of the large hound (no 38) occurred before the loop was resected on the forty-third day. This was 20 cm in circumference, and it contained 750 cc of thick, grumous, strawberry-colored fluid. The mucosa was intact, its blood vessels in the mesentery had increased from two to four times in size, and its length from 37 to 80 cm. There was a marked increase in the connective and muscle tissue in the wall of the loop. Cultures of the loop fluid grown anaerobically gave a growth of *B welchii*. One cubic centimeter of the blood serum of this animal, removed when the loop was resected, did not prevent death in a pigeon when 1 minimal lethal dose of the toxin of *B welchii* was given. Hemolysis was complete in the hemolysis tests. After the resection of the loop, the animal became well nourished within a month.

Animal 64 became very weak and emaciated in two weeks and died the day after the loop was resected. The loop was short and distended by 100 cc of tarry, grumous material, its mucosa was intact, and the wall greatly thickened by fibrous tissue. *B welchii* was isolated from fluid in it. No evidence of immune bodies against the myotoxin or the hemolysin of *B welchii* was found in the blood serum of this animal by the pigeon and hemolysis tests similar to those described.

⁵ *Tests for the Hemolysins of B Welchii in the Portal Serum, Transudate and Chyle in Obstruction*—The hypothesis that the toxin of *B welchii* is the

25 Henry (footnote 18, first reference)

toxic agent in the toxemia of acute intestinal obstruction would be materially strengthened if its presence in the abdominal transudate, the lymph from the thoracic duct or the portal blood serum of the animal with obstruction was demonstrable. This toxin is particularly suited for such studies for two reasons. If recovered in lethal quantities its antitoxin can be used to protect animals against its fatal effects, and it modifies the serums of animals so that they inhibit hemolysis.

Schonbauer²⁶ showed that the peritoneal transudate found with an obstructed bowel is toxic on intravenous injection into other animals. Stone and Firor²⁷ described experiments in which they demonstrated the toxicity of Ringer's fluid which had bathed an inflated loop of intestine containing fluid removed from another loop of obstructed bowel. The loop had been removed from the animal and it was deprived of all its blood supply. The conditions in experimental animals were not closely simulated by this experiment. Murphy and Brooks² collected the chyle from the thoracic duct of a dog a loop of whose bowel was isolated and contained fluid removed from the loop of another animal that had died from obstruction. The veins draining the loop were ligated. The fluid collected from

TABLE 3—*Data Pertaining to the Serum of the Animals Having the Resected Loops**

Dog	Date of Isolation of Loop	Date of Resection of Loop	Serum Collected	Inhibition of Hemolysis on Titration	Protection of Pigeons by Serum
65	Aug 10	Sept 5	Sept 5 Oct 6 Oct 20	Not increased Not increased	1 cc gives no protection for 1 M L D
38	Aug 21	Oct 3	Oct 3 Oct 13	Not increased	1 cc gives no protection for 1 M L D
64	Jan 21	Feb 6	Feb 6	Not increased	1 cc gives no protection for 1 M L D

* No increase of inhibition of hemolysis indicates the absence of antihemotoxin in the serum of these animals. No protection of pigeons for 1 minimal lethal dose of toxin denotes the absence in the serum of immune bodies against the myotoxin.

the thoracic duct produced death when injected into a small dog. In another experiment these workers increased the pressure in the closed loop containing toxic loop fluid removed from an animal with obstruction. A pressure of 48 inches of water was maintained. The veins draining this loop were not ligated. The chyle was collected and injected into the vein of another animal. Lethal effects were not produced.

Normal intestinal mucosa is impervious to lethal doses of the toxins of acute intestinal obstruction. Murphy and Brooks² felt that the factors that make the absorption of toxin possible were more important than the factors producing the toxin. They emphasized that the toxic materials are not rapidly absorbed through normal mucosa. The theory that increased intra-intestinal pressure is the factor that produces mucosal injury so that the toxins are absorbed in lethal quantities, stated most clearly by Murphy and Brooks,² has been stressed by Hartwell and

26 Schonbauer, L. Die Fermente in ihrer Beziehung zu gewissen Erkrankungen der Gallenblase und zum Ileus, Arch f klin Chir **130** 427, 1924, quoted by Scholefield (footnote 14)

27 Stone, H, and Firor, W M. Absorption in Intestinal Obstruction. Intra-intestinal Pressure as a Factor, Tr South Surg & Gynec A **37** 173, 1924

his associates,²⁸ Dragstedt and his co-workers,²⁹ Scholfield,¹⁴ Gatch, Trusler and Ayers³⁰ and by Morton,³¹ who recently reviewed and contributed to this phase of the question. The distention of the intestine produced by the gaseous or fluid pressure injures the mucosa by occluding its blood supply.

When I was working as an assistant of Dr. Le Count at Rush Medical College, he repeatedly pointed out to me that the necrosis in human bodies is first evident in the epithelial covering of the tips of the valvulae conniventes squarely opposite the mesenteric attachment, that is to say, at the most peripheral point in the circulation of the blood in the bowel. When the protective layer of intestinal epithelium has been functionally destroyed, absorption takes place as from the peritoneal cavity the serosa of which exerts no physiologic selective action. Gross changes are usually always seen in the mucosa, but there is no reason to believe that even in the absence of any gross or histologic changes its physiology is not profoundly affected.

When the fluid from isolated loops is filtered through a Berkefeld filter much of the lethal substance does not appear in the filtrate. Moreover, the process of filtration is difficult if heat-labile toxins such as those of *B. welchii* are to be preserved. In this experiment it was the intention to allow the wall of the bowel to serve the function of the Berkefeld filter. Long loops of bowel were isolated, and the toxic fluids were placed in them and held at a pressure a little less than the diastolic blood pressure. This pressure was produced for the purpose of damaging the mucosa, physiologically if not grossly, in order that rapid absorption would occur. The abdominal transudate and the chyle and blood from the portal vein were recovered. The animals were kept under light ether or light sodium iso-amylethylbarbiturate anesthesia during the course of the experiments. Fluids were supplied subcutaneously in the form of normal physiologic solution of sodium chloride.

McIver and his associates¹² measured a pressure of 54 mm of mercury in the unruptured isolated loops in dogs. Owings, McIntosh, Stone and Weinberg³² reported that in obstructed loops of jejunum the pressure was from 30 to 45 cm of water. Stone and Firor²⁷ found that the normal intra-intestinal pressure was 15 cm of water, whereas the pressure above an obstruction was 150 cm of water. In the present experiment a pressure of 60 mm of mercury (corresponding to 81.6 cm of water) was maintained in these long closed loops by means of either air or fluid. A Luer syringe, a mercury air valve and a mercury manometer were used to keep a constant head of pressure.

Murphy and Vincent¹ stated that the height of intoxication is apparently reached in from four to six hours when the mesenteric veins draining an occluded

28 Hartwell, J. A., Hogue, J. P., and Beekman, F. An Experimental Study of Intestinal Obstruction, *Arch. Int. Med.* **13**: 701 (May) 1914.

29 Dragstedt, Dragstedt, McClintock and Chase (footnote 6). Dragstedt, Moorhead and Burcky (footnote 4).

30 Gatch, W. D., Trusler, H. M., and Ayers, K. D. Acute Intestinal Obstruction, Mechanism and Significance of Hypochloremia and Other Blood Chemical Changes, *Am. J. M. Sc.* **173**: 649, 1927. Causes of Death in Acute Intestinal Obstruction, Clinical Applications and General Principles of Treatment, *Surg. Gynec. Obst.* **46**: 332 (March) 1928.

31 Morton, John J. The Differences Between High and Low Intestinal Obstruction in the Dog, *Arch. Surg.* **18**: 1119 (March) 1929.

32 Owings, J. C., McIntosh, C. A., Stone, H. B., and Weinberg, J. A. Intra-Intestinal Pressure in Obstruction, *Arch. Surg.* **17**: 507 (Sept.) 1928.

loop of bowel are ligated. In the experiments reported here the animals were found to fail rapidly when the intra-intestinal pressure with toxic fluids in the loop had been maintained for five or six hours. After the pressure had been maintained for five or six hours, sudden death occurred in some animals with so little warning that no time was given for the aspiration of the blood in the portal vein. In control experiments, when normal physiologic solution of sodium chloride was held under pressure in the loop, in place of the loop fluid, continuously for twelve hours or more, the animal lived for over twenty-four hours. This control was repeated in three instances with similar results.

TABLE 4—*The Titrations for Antihemotoxin*

Rabbit	Date	Amount, Cc	Serum Collected	Inhibition of Hemolysis
1 Injected with transudate from dog 17	Oct 6	1.5	Oct 6	Normal
	Oct 7	1.5	Nov 25	Not increased
	Oct 8	1.5	Dec 23	Not increased
	Oct 9	1.5		
	Oct 10	1.5		
2 Injected with portal serum from dog 17	Oct 6	1.5	Oct 6	Normal
	Oct 7	1.5	Nov 25	Not increased
	Oct 8	1.5	Dec 25	Not increased
	Oct 9	1.5		
	Oct 10	1.5		
3 Injected with 24 hour broth culture of <i>B. welchii</i>	Oct 6	1.5	Oct 6	Normal
	Oct 7	1.5	Nov 25	Complete
	Oct 8	1.5		
	Oct 9	1.5		
	Oct 10	1.5		
4 Injected with chyle from dog 24	Oct 23	1.5	Oct 23	Normal
	Oct 24	1.5	Nov 25	Complete
	Oct 25	1.5	Dec 23	Complete
	Oct 26	1.5		
	Oct 27	1.5		
5 Injected with transudate from dog 24	Oct 23	4.0	Oct 23	Normal
	Oct 24	4.0	Nov 25	Partial
	Oct 25	4.0	Dec 23	Complete
	Oct 26	4.0		
	Oct 27	4.0		

* The transudate and serum of the blood from the mesenteric veins of the loop containing loop toxin contained no hemotoxin. The transudate and the chyle from the loop containing the toxin of *B. welchii* contained toxin in sublethal quantities. This produced the antihemolysins in rabbits 4 and 5.

Loop fluid and broth cultures of *B. welchii* were held under pressure, and the transudate, chyle and blood from the mesenteric veins were collected. These were immediately injected into pigeons and into mice. No constant effects of their toxicity were found.

The following experiment was then carried out to determine the presence of sublethal quantities of the toxin of *B. welchii* in the portal blood serum and abdominal transudate. With the animal (dog 17) under sodium iso-amylethyl-barbiturate anesthesia, almost the entire small bowel was isolated by the Parker-Kerr method. The distal end was closed, and a rubber tube was fixed into the proximal end by purse-string sutures. Seven hundred fifty cubic centimeters of loop fluid removed from the loop resected from dog 38, mentioned in section 4, was introduced into this long isolated loop, and the abdomen was closed. The pressure in the loop was raised to 60 mm of mercury and held at this level. After five hours, when it became evident that the animal was failing rapidly, the abdominal

cavity was again opened, and 250 cc of portal blood was aspirated from the radicles of the portal vein draining the loop. A similar quantity of serosanguineous transudate was also removed from the abdominal cavity.

The blood and the transudate were kept at icebox temperatures, and contact with the air was prevented by an oil seal. Into the veins of a rabbit, 15 cc of this blood serum was injected for five successive days. In a similar manner a second rabbit was inoculated with doses of the transudate. After five weeks hemolysis was unaffected by the serums of these rabbits (table 4).

A control experiment was performed. Under light ether anesthesia almost the entire small bowel of dog 24 was isolated. A rubber tube, secured by purse-string sutures, was placed in the proximal end. The greatest care was used to prevent leakage into the peritoneal cavity. Three hundred cubic centimeters of the broth culture of *B. welchii*, containing 1,500 minimum lethal doses for a 350 Gm pigeon, was placed in the loop. An intra-intestinal pressure of 60 mm of mercury was held for six hours. The thoracic duct was cannulated at the beginning of the experiment and the chyle was collected. The chyle became pink from blood as soon as the pressure was raised in the isolated loop of bowel. When the life of the animal was seen to be ebbing, the abdomen was reopened. It died before aspiration of the blood from the portal vein could be done. The serosanguineous transudate was removed from the abdominal cavity and used to inoculate a rabbit by five intravenous doses of 4 cc each. A second rabbit received intravenously five doses of 15 cc each of the chyle. A third rabbit was given five doses of 15 cc each of a portion of the culture of *B. welchii* that was used in the isolated loop in this experiment. After five weeks the three rabbits were bled, and the ability of their serum to inhibit hemolysis was examined. The serums of the rabbits that received the chyle and the transudate gave as good protection against hemolysis as that of the rabbit which received the pure culture. In all of these experiments the rabbits were bled before inoculation, and the content of antihemolysins of their serums was measured. None existed in any of them.

COMMENT

After isolation of short loops of the proximal part of the jejunum in dogs death occurs as a rule in from two to five days after continuity of the gut is reestablished. The production of a closed loop is a questionable procedure because rupture of the loop with peritonitis is so commonly found after death, to which, of course no immunity is possible. If the loop is intact and if on postmortem examination no other cause for death is found, it is reasonable to assume that absorption of some of the lethal bodies within the loop has caused death. As evidence that dehydration did not occur in such animals, reported in sections 1 and 2 of this study, a clear serosanguineous transudate was found free in the peritoneal cavity. In the animals with unruptured loops and without simple obstruction the administration of the specific antitoxin should have prolonged life if the absorption of that particular toxin is the cause of death. The control animals that died from toxemia lived on the average 1.4 days longer than did the animals with a similar condition that received daily injections of 5 cc of the concentrated *B. welchii* antitoxin (table 1). The antitoxin had neither a prophylactic

not a therapeutic value, for life in the protected series should have been prolonged. Similar results were obtained by Owings and McIntosh³³

Dogs may be immunized to the toxins of *B welchii*, but there are variations in their response to inoculations with these toxins. Bull and Pritchett³⁴ found that one prophylactic dose of *B welchii* antitoxin furnished protection to a guinea-pig for twelve days when given the day before the infection occurred. Active immunization did not protect these animals against the toxins absorbed from the isolated loops (table 2)

While not pertinent to this study, it is an interesting observation that in all of the animals reported in section 1 in which simple obstruction occurred along with the isolation of the loop not one of the loops was ruptured. Some of the loops were flabby and relaxed, and their content was pasty. There was no connective tissue or muscle hypertrophy in the walls of these loops. Braeye³⁵ found that there was a latent period of ten to twenty hours in animals before the pressure in the loop was sufficient to cause necrosis and perforation. Thirty-six hours were required for toxic properties to develop in the loop fluid. In the animals with simple obstruction, mentioned in section 1, the secretion-absorption ratio within the loop was disturbed by the dehydration effects of the simple obstruction which evidently started before the end of this latent period, and therefore overdilatation of the loop did not occur. Such animals⁵ lived for an average of 13.2 days. Death was due to dehydration and starvation. If the usual lethal products of obstruction were in the loops, they were not absorbed in sufficient quantity to cause an early death. The mucosa had exerted a selective absorption of fluids, however, for the loop content in some was thick and pasty.

Dragstedt⁶ noted that if loops 25 cm. and longer are isolated, rupture of the loop does not always occur, but the animal will die in a few weeks because the liver is not able to cope with the toxic substances absorbed. The animals described in section 4 from which the loops were resected were overwhelmed by the continued absorption of the toxins of the loop content. *B welchii* was grown from each loop. It is to be expected that animals suffering from a toxemia caused by intestinal obstruction would show a marked immunity to the toxin of *B welchii* if that is the toxin absorbed. The toxemia of these animals was not due to the toxins of *B welchii*, because no specific immune bodies were produced in their serums.

33 Owings, J. C., and McIntosh, C. A. Perfringens Antitoxin and Experimental Intestinal Obstruction, Arch. Surg. 18:2237 (June) 1929.

34 Bull and Pritchett (footnote 17, second reference).

35 Braeye, L. On the Formation of the Toxic Fluid Found in Isolated Duodeno-Jejunal Loops, Bull. Johns Hopkins Hosp. 39:121, 1926.

In each of these resected loops there was a marked thickening of the connective tissue and muscular elements in their walls. This is evidence of the increased pressure within the loop. Furthermore, if the pressure within the loop had not been increased, no elongation or dilation of the loop would have occurred. The mucosa was not grossly injured, but its physiologic function was impaired for absorption of the lethal substances of the loop content had occurred, producing the gradual intoxication of the animals.

Because the toxin of *B welchii* has a powerful effect on muscle tissue, Williams⁸ expressed the opinion that the paralysis of the intestine in paralytic ileus might be due in part to the toxin of *B welchii* in the contents to which the intestinal wall is exposed in greatest concentration. The attractiveness of this idea is enhanced by the studies of Buttle and Trevan³⁶. They noted the effect of the toxin of *B welchii* on strips of the isolated small intestine of the rabbit, suspended in a bath containing 15 cc of Ringer's solution at 37 C through which air or oxygen were bubbled. Spontaneous movements of the strips of muscle occurred. The addition of the toxin of *B welchii* in sufficient amounts to the Ringer's solution in the bath caused a spasmodic contraction of the muscle. Then a diminution in the size of the spontaneous contractions occurred until they completely ceased. The previous addition of the antitoxin to the bath prevented the effect of the toxin. There is nothing in these studies to indicate that a sufficient quantity of the toxin of *B welchii* is present to produce a similar reaction in the obstructed bowel.

CONCLUSIONS

1 Dogs suffering from a toxemia caused by acute intestinal obstruction are not helped by passive or active immunization to the toxins of *B welchii*.

2 Dogs with acute intestinal obstruction produce no immune bodies for such toxins.

3 There is no evidence of the presence of the toxin of *B welchii* in the abdominal transudate or in serums of blood from the mesenteric veins of dogs with acute intestinal obstruction.

4 A method is suggested whereby the toxin of *B welchii* may be used for experimental studies of the routes of absorption of toxins from obstructed portions of the bowel.

5 There is no direct or indirect evidence that toxins of *B welchii* have any rôle in the toxemia of acute intestinal obstruction.

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³⁶ Buttle, G. A. H., and Trevan, I. W. The Action of Vibrion Septique and B. Welchii Toxin on Isolated Organs. Brit J Exper Path 9:182, 1928.

CONTINUOUS INTRAVENOUS INJECTION OF DEXTROSE IN RINGER'S SOLUTION

ITS TECHNIC AND INDICATIONS, AND A NEW
INTRAVENOUS CANNULA [†]

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In certain cases the advantages of supplying by other than the oral route not only water and the electrolytes of the blood, but caloric values, have become more and more obvious. Various modes of doing this have been much discussed ¹. Under conditions approximately normal, the administration of food, water and the necessary salts by mouth is sufficient, but in many diseases and particularly in surgical cases, this route alone is unsatisfactory, either because the stomach and intestines will not absorb a sufficient amount of nutrition and water, or because physiologic rest of these organs is indicated.

McNealy ² and McNealy and Willems ³ have shown that dextrose is apparently not absorbed by the colon, though salt solution is taken up more rapidly by the colon than by the ileum. They believe that the dextrose in enemas of dextrose solution is absorbed only if the ileocecal valve is incompetent and the dextrose is forced into the ileum, which doubtless sometimes occurs. A concentrated solution of dextrose as an enema is irritating and even the isotonic 5 per cent solution may be broken down into irritating products by the bacteria in the colon.

Matas, ⁴ in 1924, advocated the use of what he called a "continuous intravenous drip" giving 5 per cent solution of dextrose in distilled water into a vein over a period of several days.

[†] Submitted for publication, June 9, 1930.

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1 Horsley, J. Shelton. The Influence of Physiologic Research on Modern Surgery. Virginia M. Monthly **55** 790, 1929, The Intravenous Administration of Dextrose in Ringer's Solution. J. Tennessee M. A. **23** 169, 1930.

2 McNealy, R. W. Personal communication, Feb. 8, 1930.

3 McNealy, R. W., and Willems, J. D. The Absorption of Glucose from the Colon, Surg. Gynec. Obst. **49** 794, 1929.

4 Matas, R. Continued Intravenous "Drip" with Remarks on the Value of Continued Gastric Drainage and Irrigation by Nasal Intubation with Gastro-Duodenal Tube (Jute) in Surgical Practice. Ann. Surg. **79** 643, 1924.

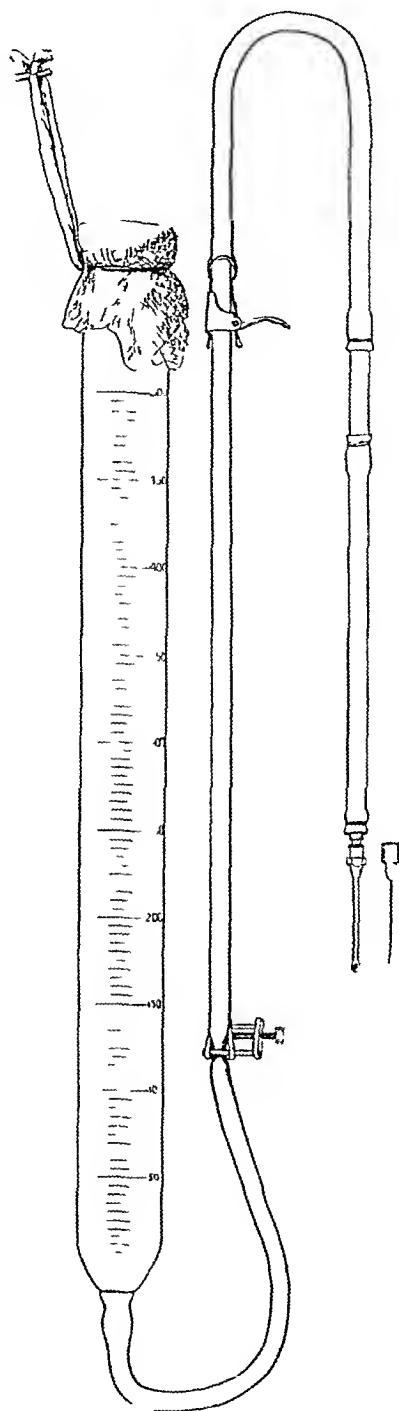


Fig 1—The buret, tube, thumb screw clamp spring clamp, metal nipple, cannula and hypodermic needle, assembled for intravenous administration of dextrose in Ringer's solution. The cannula is the only thing in the group that is original. A glass tube connection is placed at the end of the long rubber tube connecting it with a shorter segment of rubber tube. In this way it can be observed whether blood is flowing back into the rubber tube or whether there are air bubbles, and in the short segment of tube the nipple is tied.

TECHNIC

Adopting the method of Matas as a principle, we have modified the technic somewhat by using a buret 54 cm long in which 100 cc of fluid is contained in 92 cm of the length of the buret (fig 1). The flow can be regulated by a screw clamp from 75 cc an hour up to as much as it may be necessary to give quickly when shock occurs. In this way the danger of the entrance of air into the vein is largely obviated, while a constant rate of flow is maintained.

The rubber tubing should be boiled, stretched and twisted or beaten before and after being boiled, and sterile water run through it, in order to remove deposits that may cause a reaction. New rubber tubing is boiled for an hour in strong solution of soda, rinsed in running water and then boiled for an hour in tap water. At the end of the tube is a small connecting tip or metal adapter (or nipple) which fits into the hypodermic needle of a Luer syringe. A glass tube is inserted near the end of the rubber tube (fig 1).

All glass used in preparing the solution is pyrex, and new glass is thoroughly washed before using.

To the 5 per cent isotonic solution of dextrose of Matas, we add Ringer's solution. After two days the vein becomes tender, and usually by that time the patient has had sufficient amount of the solution for immediate needs. It is best then, after two or three days, to remove the intravenous cannula and give the

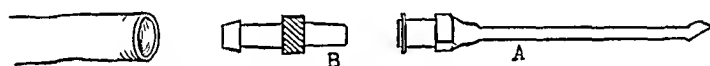


Fig 2—A shows the intravenous cannula. Note the oblique opening at the tip, which makes it easy to insert. B is the metal nipple or adapter that is tied in the tube and fits into the base of the cannula or hypodermic needle.

patient a rest for a day or two, when another vein may be utilized if necessary. In patients with large, accessible veins, and when the indications for giving the solution are for not more than ten or twelve hours, a hypodermic needle is satisfactory for the intravenous administration. For this we use a no 20 gage, stainless steel needle, $1\frac{1}{2}$ inches (37 cm) long.

We have devised a cannula which is employed when the solution is to be given for more than ten or twelve hours. This cannula measures 56 cm in length and has at its tip an oblique opening that permits it to be introduced into the vein as easily as a grooved director (fig 2). Its lumen is large and clear throughout, which lessens the chances of its being stopped up. The base of the cannula is ground to fit an ordinary Luer syringe, so by merely disconnecting the metal adapter or nipple on the tube through which the intravenous solution flows the cannula is at once available for transfusion of blood by the syringe method. After the transfusion, the adapter may again be inserted into the cannula, and the dextrose and Ringer's solution can be continued.

The advantages of Ringer's solution were demonstrated by Ringer himself when he first used physiologic solution of sodium chloride for maintaining the isolated heart of a frog or a turtle and found that after this solution had become almost ineffective the addition of a small amount of calcium would cause marked contraction. Ringer's solution contains 0.7 per cent sodium chloride, 0.03 per cent potassium chloride

and 0.025 per cent calcium chloride in distilled water. It has the mineral elements of the plasma of the blood (sodium chloride, potassium chloride and calcium) in approximately the same ratio as found in the blood serum. Potassium seems to cause a relaxation of the heart muscle and calcium contraction.

Calcium not only tends to stimulate the heart, but in such amounts as in Ringer's solution is not injurious to the subcutaneous tissues. In one patient in whom this solution was used, the needle slipped from the vein and there was a considerable amount of infiltration in the tissues of the forearm, but on withdrawing the needle the solution was readily absorbed without any ill effects. Ringer's solution may be employed for hypodermoclysis. Of course, greater concentrations of calcium are very irritating to subcutaneous tissues. If there is an indication for increasing the calcium in the blood, as in slow clotting or in jaundice, additional calcium may be injected with a hypodermic syringe into the tube while the dextrose and Ringer's solution are flowing. This is better than pouring it into the buret, for when injected it is quickly washed out of the vein.

Calcium also retards the passage of fluids from the vascular system by decreasing the permeability of the blood and lymph vessels.⁵ If too strong, its effects in this respect may be deleterious, particularly to the function of the kidneys, but in the strength in Ringer's solution, this tendency of calcium to hold the solution in the vascular system is helpful in shock, aside from the stimulating effect of calcium on the heart.

Five per cent dextrose is approximately an isotonic solution, and while this can usually be utilized by the tissues, it is advisable in a weakened patient to add some insulin, about half of the amount necessary for the complete conversion of the dextrose. We inject into the tube 10 units of insulin for every 500 cc of dextrose in Ringer's solution as the solution is flowing. The use of insulin with dextrose solution given intravenously has been advocated by Ort,⁶ Thalhimer,⁷ Fisher and Snell,⁸ Andrews and Reuterskiöld,⁹ and others.

Dextrose found on the market in bulk is not chemically pure. While it may be labeled "chemically pure quality," a glance at the printed analysis will show some impurities that may cause a reaction. The

5 Sollmann Torald. A Manual of Pharmacology, ed 2, Philadelphia W. B. Saunders Company, 1922, p. 795.

6 Ort, M. Treatment of Post-Operative Acidosis by Means of Insulin, *Arch. franco-belges de chir.* **27**: 994, 1924.

7 Thalhimer, W. Insulin Treatment of Postoperative (Nondiabetic) Acidosis, *J. A. M. A.* **81**: 383 (Aug. 4) 1923.

8 Fisher, D. and Snell, F. The Insulin Treatment of Preoperative and Postoperative Nondiabetic Acidosis, *J. A. M. A.* **82**: 699 (March 1) 1924.

9 Andrews, Edmund and Reuterskiöld, Knute. Dangers in the Postoperative Use of Insulin, *Surg. Gynec. Obst.* **47**: 665, 1928.

dextrose solution in ampules seems to be purified to such an extent that it is much less likely to cause a reaction

Ringer's solution may be made from tablets and freshly distilled water, and the dextrose added later. However, we have had prepared an ampule which is much more convenient and the purity of which seems to be satisfactory. The ampule contains 100 cc of a solution of dextrose and Ringer's solution in such a concentration that when added to 400 cc of freshly distilled water a solution of 500 cc of 5 per cent dextrose and normal Ringer's solution results. The contents of an ampule are poured into a flask, 400 cc of freshly distilled water is added, the flask is shaken and the solution is ready for use. In whatever way the solution is prepared, freshly distilled water—certainly not more than twenty-four hours old—should be used.

Precautions as for any intravenous administration should be taken in expelling the air as far as possible from the tube. If a hypodermic needle is used, it is introduced attached to a syringe, which is half filled with physiologic solution of sodium chloride, and when blood is drawn back freely into the syringe, showing that the needle is in the vein, the constriction on the arm is released, the needle is strapped in position with adhesive plaster, the syringe is detached, and the connecting nipple in the rubber tube from the buret is attached to the hypodermic needle with the solution flowing. When the cannula is used, a short incision, usually transverse, is made over one of the large veins just below the bend of the elbow, and the cannula is inserted in the usual manner. It may be inserted while connected with a syringe, as with the hypodermic needle, though this is not essential, it would prevent, however, reflux of blood into the cannula if the clamp on the vein should become displaced, and so render clotting in the cannula less likely to occur.

It is important to see that there is a constant flow through the cannula. If it becomes plugged, the flow may sometimes be reestablished by elevation of the buret, which increases the pressure, if this does not open the cannula, the connecting nipple is detached and the clot loosened with a probe and sucked out with a syringe. If the obstruction is due to clotting in the vein, the cannula should be removed and inserted elsewhere.

We now use the ampule of prepared concentrated dextrose and Ringer's solution, but of course the Ringer's solution may be made separately and an ampule of dextrose added later, or the Ringer's solution may be used alone if there is a contraindication for dextrose as in diabetic patients. If tablets for Ringer's solution are used a sufficient amount is thoroughly dissolved in 50 cc of distilled water and this solution is filtered through three thicknesses of fine white silk

cloth, using glass funnels only. New cloth is always thoroughly washed before using. The 50 cc of solution is added to 1,950 cc of distilled water, making 2,000 cc, which is boiled slowly for ten or fifteen minutes. The solution is dated and should not be used if over twenty-four hours old.

The rate of flow is regulated by a thumb screw clamp. Hot water bottles are hung around the buret and over the tube, though it is probably not so important to maintain accurately the temperature of the solution as was formerly thought. The small amount of fluid entering the body cannot affect its temperature greatly if there is a variation of only a few degrees.

For patients who are edematous or whose renal function is greatly impaired, salts should not be used. In such instances, 5 per cent dextrose alone may be administered. When the function of the kidneys is markedly affected, the strength of the dextrose can be increased to 10, 15 or 20 per cent. The giving of a very concentrated dextrose solution, however, may not be entirely without danger. Certainly it causes a marked irritation of the vein and draws fluid rapidly from the tissues. Higher concentrations, such as 20 per cent or more, should be given rather quickly.

The rate at which the intravenous flow of dextrose and Ringer's solution should be maintained depends entirely on the conditions. In hemorrhage or shock, it should be rapid enough to secure almost a normal blood pressure within a short time. In shock, when the blood pressure is low, it is impossible to overload the heart until the blood pressure has approximated what is normal for that individual. The lumen of the cannula will permit a rapid flow, and as much as 400 or 500 cc of the fluid can be given in a few minutes, until the blood pressure is within ten or fifteen points of the patient's normal pressure. Then it is cut down to a rate of 150 or 200 cc an hour and maintained until the clinical condition is satisfactory. When hemorrhage is marked or after shock has been well established, dextrose in Ringer's solution may not be entirely effective, but it can be utilized until a donor is secured for a transfusion of blood. It is much better for the patient to have the blood pressure kept up even temporarily by a solution that contains no abnormal constituents of the blood than to have a marked drop in blood pressure continue over some time with its subsequent deleterious effect on the brain, kidneys and vital organs.

For other conditions than shock or hemorrhage the solution should be given at a rate of from 75 to 200 cc per hour.

When the hemoglobin is below 45 or 50 per cent the oxygen-carrying power of the blood is greatly affected and even though dextrose in Ringer's solution is beneficial it would doubtless be better to give a transfusion of blood and then continue the solution.

In spinal anesthesia there is often a marked drop in blood pressure. We make a practice of beginning intravenous injection of dextrose in Ringer's solution immediately after the spinal anesthesia, and before the operation is commenced. Either a needle or a cannula can be used, depending on the conditions. If it is to be a long operation, particularly if it is resection of the stomach with the indications for supplying nutrition, water and the electrolytes for some days, or if there is the possibility of the needle becoming obstructed, a cannula is inserted. If the blood pressure begins to fall, the clamp on the tube is opened widely and a small amount of epinephrine solution is injected into the tube with a hypodermic syringe while the solution is running. This will quickly bring the blood pressure up several points, where it can usually be maintained.

When there is much vomiting, as in intestinal obstruction, the dextrose and Ringer's solution should be given, and an additional amount of sodium chloride may be added as recommended by Haden and Oll¹⁰.

In the loss of pancreatic juice, as with a duodenal fistula, or in obstructive vomiting when the pancreatic juice is regurgitated into the stomach, this solution is very effective. In malnutrition or after operations in which it is desirable to give rest for the stomach and intestinal tract, the continuous administration of dextrose and Ringer's solution is indicated. In the vomiting of pregnancy it is beneficial. In peritonitis and sepsis, it is very satisfactory. In diarrhea and dysentery, when there is marked dehydration, it is excellent. In toxic goiter and hyperthyroidism, it acts as a buffer for the tissues that are burned up by the increased metabolism, and in this way the tissues are protected from excessive oxidation, so it is indicated after operations for hyperthyroidism.

One gram of dextrose equals 3.75 calories, so in giving 3,600 cc of a 5 per cent solution of dextrose in twenty-four hours, at the rate of 150 cc an hour, we supply 675 calories. It is obvious that this puts the patient in a better condition, even though the calories are not up to normal, than if he were not absorbing nutrition, or if it were attempted to force nutrition through the bowel, the function of which was impaired from weakness or from the operation.

In patients who are vomiting or who have fistulous openings or diarrhea, the discharge of body fluids is a kind of safety valve, and more of the solution may be given than if these conditions were not present. If the patient is thin and the blood pressure high, the solution should be used with caution. When large quantities of this or of any

¹⁰ Haden, R. L., and Orr, T. G. Use of Sodium Chloride in the Treatment of Intestinal Obstruction, *J. A. M. A.* 82:1515 (May 10) 1924.

intravenous solution are given for several days, "water sickness" sometimes appears. It comes on gradually, the early symptoms being puffiness of the lower eyelids, watering of the eyes and vomiting of clear or bile-stained fluid. Discontinuance of the solution is quickly followed by disappearance of the symptoms.

The administration of this dextrose and Ringer's solution often permits operations such as excision of the rectum to be done in one stage instead of in two or more. By keeping the solution flowing slowly and turning on more when the blood pressure becomes lower, the operation can usually be completed in one stage. The advantages of removing all of a cancer in one stage as a block dissection instead of in two stages are obvious. If at the end of the procedure the patient still shows symptoms of shock, a transfusion of blood can be done, and the dextrose and Ringer's solution can be continued.

We have practiced the general principles of the technic herein described for about six years, beginning soon after the publication of the paper by Matas⁴. It has been employed in about 750 cases. The reactions have been few, and in the past two years since using the purified dextrose in ampules there have been only three or four reactions that could be attributed to the intravenous injection and these have not been followed by bad effects.

THE FATE OF THE CORTICAL BONE GRAFT *

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AND

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Although many tissues of the body are commonly transplanted and recognized to retain their viability and regenerative power, comparatively little is known of the histogenetic properties in transplanted bone

The object of this series of experiments was an attempt to determine whether autoplasmic cortical bone when grafted into cortical bone in its normal relationship becomes a living integral part of the skeleton or whether it simply acts as a temporary scaffold for the deposit of new bone cells that fills in the defect with new bone

By microscopic examination alone it is impossible to determine whether the transplant has lived in bulk or whether it has died and served only as a framework for the deposit of new bone

In botany, where plant life easily lends itself to this variety of experimentation, it is positively proved in tree grafting that the graft lives in bulk, grows and produces limb and fruit of the variety of the graft. Why should not a bone graft live and grow in the human skeleton in a similar manner?

For this series of experiments advantage was taken of the fact that in an animal fed on a diet containing sodium alizarin sulphonate (synthetic madder root dye) all new bone developed while the dye is being administered is colored "madder red," while the bone formed before the dye is given remains the natural color. This makes a striking distinction in the color of the bone developing from a definitely fixed time

To get the control in color, two animals were used for each experiment. To have the transplantation as nearly autoplasmic as possible, two pups from the same litter were used in each experiment

The first pup was given a small amount of alizarin in its food, beginning as soon as it was weaned, so that its skeleton would be well

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* Read before the Medical Research Club of the University of Illinois, May 14, 1930

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colored at the time of the transplantation of the graft. The dye was continued in its food after the transplantation of the graft until the animal was killed.

The second pup was given ordinary diet without dye, both before and after the transplantation of the graft.

The scheme of the investigation was as follows:

1. If on exposure of the area of transplantation on the living animal and removal of the periosteum under ether, the graft was demonstrable and oozed blood freely from its surface, then it evidently was living bone.

2. If in the dog the skeleton of which was dyed, an undyed transplant was grafted and the dyeing process continued for a period long enough for any metamorphosis in the graft to be completed, and on exposure of the graft it was found to have only a very faint tinge of pink, such as would be produced by the natural increase of new bone cells in a young dog, and if this graft was entirely surrounded by dark red bone, then evidently the graft as transplanted had practically become an integral part of the skeleton of its host.

3. Alizarin has the specific action of dyeing developing bone cells. When a bone cell reaches maturity, the dyeing process ceases, the cell becomes calcified, and the pigment is sealed in. The color remains permanent during the life of the bone cell. At the death of the bone cell the mineral salts are absorbed, the pigment is liberated and dissipated, and the color disappears. Therefore, if in the dog with an undyed skeleton a dyed transplant was grafted and no alizarin was given after transplantation, and the life of the animal was preserved for a sufficient length of time for any metamorphosis in the graft to be completed, and on exposure of the graft, it was found to consist of dark red bone entirely surrounded by natural colored bone, evidently the graft colored as transplanted was living bone and had become an integral part of the skeleton of its host.

Throughout the experiments, only young healthy dogs were used, and all features of modern aseptic surgery were observed. The animals used were in the growing age, and transplantation was done only in those from the same litter.

EXPERIMENTAL PROCEDURE

The experimental procedure and histogenetic observations noted were as follows:

EXPERIMENT 1 (dog 1).—This dog was fed alizarin for sixty days. At this time a transplant from the cortical layer of the frontal bone 1 by 2 cm. was removed and interchanged with similar bone from dog 2, which had received no alizarin in its diet. Alizarin was continued for 250 days after the initial operation, then the animal was operated on again.

It was anesthetized with ether, and the area of original operation exposed. All flesh and periosteum were removed.

The graft was apparent as an area of natural colored bone surrounded by dark red bone. There were minute bleeding points evenly distributed over the entire surface of the graft.

After observation of the graft and surrounding bone in the living dog, it was killed. The part of the skull containing the transplant was removed and immediately examined. It showed an inset of natural colored bone, of the size, shape and thickness of the transplant and, surrounded by dark red bone, grafted to the surrounding bone. The cortical bone at the edge of the graft and the cancellous bone underneath it were dyed dark red. There was a sharp line of distinction in color between the graft and the surrounding bone.

On close inspection of the cut surface of the transplant a very faint tinge of pink was seen, showing that there had been the natural growth of new bone cells in the graft after transplantation.

EXPERIMENT 1 (dog 2)—This dog received the regular diet without alizarin. A transplant from the cortical layer of the frontal bone, 1 by 2 cm., was removed and interchanged with similar bone from dog 1, which had received alizarin for sixty days prior to operation. The diet was continued as before operation. This dog was operated on again 254 days after the first operation. The dog was anesthetized with ether, and the area of original operation was exposed. All flesh and periosteum were removed.

The graft was apparent as a dark red area surrounded by natural colored bone. There were minute bleeding points evenly distributed over the entire surface of the graft.

After examination of the graft and surrounding bone in the living dog, it was killed. The part of the skull containing the transplant was removed and immediately examined. The graft was apparent as an inset of dark red bone, of the size, shape and thickness of the transplant, surrounded by bone of natural color. A cross-section of the transplant showed it to be well grafted to the surrounding bone. There was a sharp line of distinction in color between the graft and the surrounding bone.

EXPERIMENT 2 (dog 3)—This dog was given alizarin for seventy-two days. At the end of this period a transplant from the cortical layer of the frontal bone was removed and interchanged with bone of similar location and dimensions from dog 4, which had received no alizarin. The diet containing alizarin was continued for 249 days, when it was operated on and killed.

The observations at operation and examination of the specimen were in detail as those found in dog 1, in the previous experiment.

EXPERIMENT 2 (dog 4)—This dog was not given alizarin. A transplant from the cortical layer of the frontal bone was interchanged with one from dog 3. The animal was operated on and killed after 249 days.

The observations at operation and examination of the specimen were in detail as those found in dog 2, in the previous experiment.

EXPERIMENT 3 (dog 5)—This dog was fed alizarin for eighty-three days. A transplant from the cortical layer of the frontal bone was interchanged with one from dog 6, which had received no alizarin. The alizarin was continued for 300 days, after which the animal was operated on and killed.

The observations were in detail as those in dogs 1 and 3 in the previous experiments.

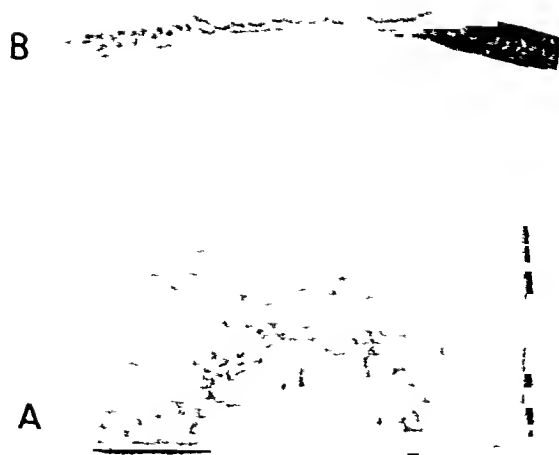


Fig 1

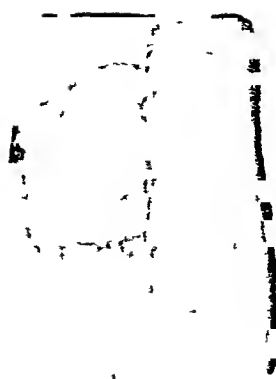


Fig 2



Fig 3

Fig 1 (dog 1) — *A* shows graft as an inset of bone of natural color in a field of dyed bone, after 250 days. *B*, a cross-section through the specimen.

Fig 2 (dog 3) — Graft as an inset of bone of natural color in a field of dyed bone, after 249 days.

Fig 3 (dog 5) — Graft as an inset of bone of natural color in a field of dyed bone after 300 days.

EXPERIMENT 3 (dog 6) —This dog was not given alizarin. A transplant from the cortical layer of the frontal bone was interchanged with one from dog 5. The animal was operated on and killed after 300 days.

The observations at operation and examination of the specimen were in detail as those found in dogs 2 and 4 in the previous experiments.

SUMMARY

From this series of experiments it is our opinion that an autoplasmic cortical bone graft transplanted aseptically into cortical bone with perfect mechanical adaptation and fixation will heal by primary intention, with preservation of the vitality of the graft.

VACCINATION AGAINST PERITONITIS IN SURGERY OF THE COLON

FURTHER REPORT

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AND

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ROCHESTER, MINN

In December, 1928,¹ we reported before this association, sixty-one cases of tumor of the colon resected after the patients had had the benefit of cooperative management of a medical and a surgical service. Among the details of the treatment, intraperitoneal vaccination was considered one of the essentials. The striking reduction in mortality in this group over the control group, in which operation was performed by the same surgeons under the same circumstances, increased our belief that this was an important detail in guarding against the peritonitis which is the customary cause of death in more than half of these cases.

Our efforts to ascertain more closely the merits of intraperitoneal vaccination, as applied clinically, were stimulated by the experimental work of Herrmann² in 1928. We carried this work forward and by Oct 1, 1929, we had increased to 300 the series of cases in which vaccination and operation had been done. In addition, we have been able to correlate some experimental results obtained by Kellum³ working in Rosenow's laboratory, which suggest that the introduction of a mixed vaccine of colon bacilli and streptococci has a very important bearing on mortality statistics by increasing the immunity to infection and thus raising the threshold of surgical safety.

Peritoneal contamination has always been considered one of the most serious menaces to successful surgical treatment of the colon, and any agent which obviates peritonitis or militates against it is a highly desirable adjunct to the surgeon's armamentarium. It is evident that vaccine, as a single step, probably would fail to accomplish satisfactory

¹ Submitted for publication, Jan 20, 1930

² Read before the Southern Surgical Association, Atlanta, Ga., Dec 10, 1929

From the Division of Surgery and Division of Medicine, the Mayo Clinic

1 Rankin, F W, and Borgen, J A. Carcinoma of the Colon. Intraperitoneal Vaccination by Mixed Vaccine of Colon Bacilli and Streptococci, Arch Surg **19** 906 (Nov) 1929

2 Herrmann, S F. Experimental Peritonitis and Peritoneal Immunity, Arch Surg **18** 2202 (May) 1929

3 Kellum E L. Unpublished data

results, and that it must be combined with other cooperative measures. The reasons for peritonitis developing so frequently group themselves mainly under three headings (1) the peculiar conformation of the large bowel, which differs from the small intestine anatomically and physiologically, (2) the increased permeability of the large bowel when attacked by malignant disease, due either to its peculiar structure or to mucosal injury produced by large ulcerating carcinomas, and (3) the general condition of the patient as evidenced by the debilitated dehydrated and generally lowered resistance of patients who harbor neoplasms.

The anatomic construction of the large and the small intestinal canals, differs considerably, and thereby, in technical maneuvers on the large bowel, influences are brought to bear which do not pertain to the upper part of the gastro-intestinal tract. The musculature of the large bowel is markedly thinner than that of the small intestine, and the tunica propria, which is beneath the endothelial layer and which contains lymphatic channels as well as blood vessels, is frequently replaced by fat. The powerful peristaltic action of the large bowel, which normally is greater than that of the small intestine, likewise increases the strain on suture lines, with occasional concomitant leakage and abscess formation or peritonitis. The inconstant blood supply of the large bowel and the occasionally independable anastomosis between the arcs, likewise is sometimes a factor in causing a spot of lowered resistance which may result in contamination. These anatomic factors, plus the increased permeability of the large bowel under obstructive conditions, bear a direct relation to contamination. Given a slow, encroaching growth which encircles the lumen of the large bowel and stenoses it gradually, one finds increased peristalsis as the resistance progresses, and a greater attempt on the part of the intestine to empty itself. If this occurs in the presence of an ulcerating and fungating neoplasm, the infection is much more readily spread to the adjacent tissues and is indeed demonstrable in peritoneal tissues at a considerable distance from the original growth. The mucosal injury and the stenosis at the site of the growth are the two factors which increase permeability and spread contamination. Neither factor alone is sufficient, but the combination as it is usually found in cases of malignant growths of the colon is a constant and necessary factor in subsequent infections. We have a fixed idea that manipulation of colonic growths with spreading of the peritoneal infection already present is a greater source of potential danger than leakage at the suture line or other technical factors which so often are blamed for failures in operations.

Recently we have made cultures from eighteen malignant colonic lesions immediately after their extirpation and the results obtained seem

to bear out the assertions made relative to the infection in the peritoneal tissues in immediate juxtaposition to the growth. The tumor was removed by surgical resection under the strictest aseptic precautions, the peritoneal surface was immediately seared with a hot spatula after the usual method of searing tissues for culture. A sterile Pasteur pipet was inserted just under the serosa of the tumor and another just into the outer edge of the tumor, material was aspirated and immediately transferred to dextrose-brain broth (Rosenow's medium) and shake cultures were made with blood agar. The lesions of the bowel from which cultures were made included carcinomas of the cecum, ascending colon, hepatic flexure, splenic flexure, descending colon, rectosigmoid and rectum. In cultures of thirteen lesions, only short-chained, green-producing streptococci and colon bacilli grew, in cultures of three lesions, no bacteria grew, in cultures of one lesion only, gram-negative bacilli resembling colon bacilli grew, and in another, staphylococci, and gram-negative and large gram-positive bacilli grew. Thus, it is seen that in 72 per cent of the lesions cultured, only green-producing streptococci and colon bacilli grew, in 17 per cent no bacteria grew, and cultures of the other 11 per cent were indeterminate. This would certainly suggest that the vastly predominating bacteria in and around malignant lesions of the colon are streptococci and colon bacilli.

That the visceral peritoneum acts protectively against these organisms is further suggested by the following facts. Similar culture mediums to those which have been described, inoculated from material obtained from thirteen patients in whom the serosa over the tumor was cultured by swabbing with a sterile cotton swab immediately after opening the abdomen and exposing the tumor, remained sterile in most instances. Staphylococci, large gram-positive bacilli, diphtheroid organisms and indifferent streptococci, obviously of no significance, grew in a few instances.

With the knowledge that streptococci and colon bacilli are the chief offenders in and around malignant colonic lesions, and owing to the fact that the visceral peritoneum acts protectively, it would seem of vital importance to establish a specific or nonspecific relationship between intraperitoneal vaccination and the mechanism of its protection. At first thought, we would say there is specific local and possibly also general immunity against the two chief offending bacteria. This view must be maintained unless very positive and convincing proof is brought forth to the contrary.

The work of Morton⁴ suggests that various substances can be used to immunize the patient intraperitoneally against lethal doses of hemo-

⁴ Morton, H. B. Nonspecific Peritoneal Immunization, Proc. Staff Meet., Mayo Clin. 4: 209 (July) 1929.

lytic streptococci. He used bacterial filtrates, dextrose and a physiologic solution of sodium chloride and found stimulation of peritoneal defense with all. He also noted that the mechanism of such local immunity was by local peritoneal irritation, which called forth numerous macrophage cells, and phagocytosis of the hemolytic streptococci was carried on by these. However, the number of his animals was too small to allow of the conclusion that these nonspecific substances would serve as well as the vaccine produced from the organisms which seemed to be at least in part responsible for the etiology of peritonitis in human beings.

An outstanding detail of Morton's studies is the fact that some immunity can be produced in twenty-four or forty-eight hours, but much greater and more nearly complete immunity results from periodic injections over a period of six days. It would seem, then, that if enough rabbits were given injections of such substances as the streptococcus-colon bacillus vaccine, dead typhoid bacilli or milk and dextrose if their omenta were sectioned and the peritoneal exudate studied for degree and extent of phagocytosis, and if animals were protected by these methods and then similar lethal doses of living streptococci and colon bacilli were injected into each and their peritoneal cavities and the degree of reaction studied, and if agglutinins could be demonstrated in the blood of these rabbits, the problem of what form of immunizing agent it would be best to use should be answered. Furthermore, after resection, a comparison of specimens of omenta or colonic mesenteries of patients who had had vaccine and those who had not, might give definite clues as to the nature of the mechanism of peritoneal immunity in the human being. A large series of freshly resected malignant lesions from patients who had had vaccine and from those who had been operated on without vaccine was studied for cellular infiltration in and about the tumor. Only the usual lymphocytic infiltration occurred. It was evident, therefore, that if any change was to be seen in the vaccinated and nonvaccinated patients, sections of omentum or mesentery distant from the malignant lesion should be studied. A collection of such specimens is being made, and a study of animals along similar lines is being carried out. All of the reagents produced leukocytosis in rabbits. The leukocytosis from the streptococcus-colon bacillus vaccine is by far the most marked. There was no gross evidence of peritoneal reaction in any of the rabbits which received whole autoclaved milk. In only one of those which received dead typhoid bacilli was there any gross evidence of peritoneal reaction. In 75 per cent of the rabbits which received the streptococcus-colon bacillus vaccine there was gross evidence of peritoneal irritation in the form of exudation of material grossly resembling fibrin.

Into five series of rabbits (four in each series) were injected intraperitoneally after the methods described elsewhere antiperitonitis vac-

cine, whole autoclaved milk, suspensions of killed typhoid bacilli like those used for fever therapy, hypertonic dextrose solution, and sodium chloride solution, respectively. The four animals were killed twelve, twenty-four, forty-eight and seventy-two hours, respectively, after injection and it was noted that the cellular infiltration both with polymorphonuclear leukocytes as well as macrophage cells of the omentums of the rabbits was greatest in those which had had the antiperitonitis vaccine mixture of streptococci and colon bacilli.

Other series of rabbits, all of the same size and general appearance, and all seemingly in good health, were given intraperitoneal injections of the same materials: vaccine of a mixture of streptococci and colon bacilli, killed typhoid bacilli, hypertonic dextrose solution, sodium chloride solution and whole autoclaved milk. The injections were made according to methods described by Heimann and found suitable as described elsewhere, and forty-eight hours after the last intraperitoneal injection large doses of equal suspensions of living green-producing streptococci and colon bacilli were given.

All the rabbits that had the injections of milk died, half of the rabbits that had typhoid bacilli and half that had sodium chloride solution died, all with fulminating generalized fibrinopurulent peritonitis. None of those that had been given antiperitonitis vaccine and none of those receiving dextrose died.

These experiments are being continued by adding to the numbers of animals and varying the intervals between injections. The results will be reported in detail by Kellum.

The experimental, as well as the clinical, evidence is in favor of rather transient peritoneal immunity. However, the intraperitoneal route of the injection is of vast importance. As in animals, the most favorable time for resection seems to be forty-eight hours after the second intraperitoneal injection of the vaccine.

In several of the cases in which the patients died, vaccine was given in anticipation of resection, and then, because of local fixation or the situation of the lesion, only colostomy was performed. Subsequently, it was thought that perhaps the vaccine from the first procedure would suffice, and resection was undertaken without further vaccination. Others, treated similarly, had much severer postoperative courses than those who received vaccine in the routine way preoperatively, that is, two and five days before resection.

It has become necessary or has seemed wise, occasionally, to operate on the patient within twenty-four hours after the administration of the vaccine, the peritoneal injection and hyperemia in these instances have been noteworthy. On several occasions the surgeon has thought of the possibility of colitis because of the hyperemia of the serosa of the colon,

this suggests the value of drawing the blood supply to these parts and with it, of course, increased numbers of phagocytic types of cells

The method of preparing the vaccine and its administration seem important. The organisms used for the vaccine are procured from the peritoneal exudate in a case of peritonitis. The vaccine prepared from the streptococci and colon bacilli so obtained is injected, in physiologic solution of sodium chloride, with a dulled spinal puncture needle, into the peritoneal cavity.

There are other important preoperative factors that make for a smoother convalescence and lower mortality rate in these cases of malignant disease of the colon. They include thorough cleansing of the large intestine, and particularly relief from obstruction. This has been accomplished in various ways, including the giving of a residue-free diet consisting primarily of fruit juices and candy, up to 3,000 calories are consumed in each period of twenty-four hours. Some laxative is given, and the colon is irrigated with physiologic solution of sodium chloride twice daily. At times this is best accomplished by giving such irrigations with the patient in the knee-chest position. Occasionally, hot abdominal stupes and withholding of food by mouth become necessary. Other measures of rehabilitation have included blood transfusions, control of carbohydrate metabolism and of urinary dysfunction, prevention of infection of the upper respiratory tract, and all other measures of seeming importance in preparation of a patient for an extensive surgical maneuver. Spinal anesthesia, also, holds a place of primary importance in any consideration of surgical procedures on the colon. Experimental laboratory and clinical experience with these cases suggests that intra-peritoneal vaccination is one of the most important steps in cooperative management of patients with malignant lesions of the colon.

The basis of this report is the 222 cases in which vaccine was given between Jan. 1 and Oct. 1, 1929, and fifty-eight cases in which operation was done in the course of these months, for similar conditions, and in which vaccine was not given.

A review of the eleven deaths from peritonitis, which occurred among the 222 patients operated on, suggests consideration of types of operations in cases included in this review. The patients operated on had all forms of surgical maneuver that are applied to the colon at the Mayo Clinic. Many of them, of course, underwent two or more major surgical procedures as in all the graded resections. For this reason, the small number of eleven deaths from peritonitis is noteworthy. The tabulation shows the types of disease and the surgical procedures attempted in the eleven fatal cases.

Although these eleven cases include several in which the usual procedures in operating on the colon at the Mayo Clinic were employed

cases necessitating unusual procedures are also listed. Some very extensive operations were required in greatly debilitated patients.

The fifty-eight patients with malignant lesions of the colon operated on during the same period, who did not receive vaccine, had lesions of similar situation and nature as those of the 222 who received vaccine. Of the fifty-eight patients, thirteen died of peritonitis, the operative procedures on the thirteen included four abdominoperineal resections, one Mikulicz operation (first stage), one ileostomy, one cecostomy, one colostomy, one ileocolostomy, three posterior resections of the rectum and one secondary resection of a lesion of the left part of the colon.

Summary of Eleven Cases of Peritonitis

Case	Age	Sex	Type and Situation of Lesion	Factors Relating to Risk	Anesthetic	Surgical Procedure
1*	67	M	Carcinoma of rectum	Age, peritoneum opened widely	Regional, amytal†	Posterior resection after preliminary colostomy
2	60		Carcinoma of transverse colon	Obesity, complete obstruction, abdominal stipes necessary, omentum in ventral hernia, extensive operation	Spinal	Ileostomy and first stage of Mikulicz
3	70	M	Carcinoma of rectosigmoid	Fixed tumor with obstruction, much manipulation in determining possible operability	Spinal	Colostomy
4	74	M	Carcinoma graded 3 of rectosigmoid	Age, high grade of malignancy, extensive operation	Spinal	Colostomy and anterior resection
5	48	F	Carcinoma graded 3 of rectosigmoid	High grade of malignancy, lesion fixed and obstructive, obesity and hypertension	Spinal	Colostomy and interior resection
6	44	M	Carcinoma of rectosigmoid	Fixation of lesion and soiling of field	Regional, amytal‡	Posterior resection after preliminary colostomy
7	48	M	Lymphosarcoma, 15 by 10 by 10 cm of ascending colon	Local perforation of growth two days before operation	General	Resection of right half of colon for perforated lesion
8†	30	M	Carcinoma of transverse colon	Obesity, loss of 35 pounds in weight in short time, hemoglobin 36 per cent, intussusception of large lesion incorporating the stomach	Spinal	Colostomy
9	43	M	Carcinoma of rectum		Spinal	Colostomy and combined abdominoperineal resection
10	47	M	Carcinoma of rectosigmoid		General	Anterior resection, lesion brought out as in Mikulicz end to side anastomosis
11	44		Carcinoma graded 3 of transverse colon	High grade of malignancy, rapid loss of weight, small bowel attached to growth	Spinal	Resection for obstruction, forced resection of part of small bowel

* Contributing lethal factor, cellulitis

† Contributing lethal factor, bronchopneumonia

‡ Iso amylethyl barbituric acid

COMMENT

These studies emphasize the value of preoperative protection against peritonitis in procedures in which resection of parts of the large intestine are involved. That the intraperitoneal vaccination is one of the major parts of our preparation is demonstrated by the following facts. In the same week the same surgeon has operated on two patients of the same general build and age and otherwise offering a similar surgical risk with lesions in identical situations, and has employed the same surgical maneuver, but one patient received vaccine and the other did not. The first patient died within five or six days from generalized peritonitis, the second made a smooth, uneventful recovery. Except for the vaccine the preoperative measures in both cases were the same.

It has been amply demonstrated that protection against lethal peritonitis can be established in animals. The relatively transient nature of such immunity is noteworthy. The time element between vaccination and operation is important. The amount of vaccine injected has less significance, but is important. The systemic reaction of the patient is often moderately severe, but endures only a short period and is never alarming.

That the logical preventive reagent is a vaccine prepared from streptococci and colon bacilli is suggested by the predominant presence of these organisms in the exudate in fatal cases of peritonitis and their vast predominance in and around malignant lesions of the large intestine. Future experimental work and the method of trial and error should establish the best reagent for this mechanism of protection against peritonitis.

ILEOCECAL CYSTS *

EARLE DRENNEN, M D

BIRMINGHAM, ALA

Cysts of the ileocecal region constitute a definite pathologic and surgical entity. That they are enterogenous developmental cysts, there can be no doubt. While the nature of these cysts is now well understood, the cause of their origin remains obscure. In many of the lower animals, the arrangement of the cecal pouches is suggestive. Ileocecal cysts are rare. A search of the literature yielded but twenty cases. It is evident, however, that many cases have been overlooked. With a growing appreciation of the condition, one may expect a marked increase in the number of cases reported.

Cysts and diverticula of the intestine apparently escaped the notice of the older pathologists.

In the small intestine, diverticula and cysts are found between the leaves of the mesentery, where the vessels pierce the wall of the intestine, leaving a point of lessened resistance.

In the large intestine the mucosal hernias or diverticula escape into the fatty appendices epiploicae, also a spot of lessened resistance. Owing to the fact that these diverticula are covered with fat, it is easy to understand their being overlooked. Roentgen examination often reveals them when their presence has not been suspected. About 5 per cent of all routine gastro-intestinal roentgen examinations show diverticula.

In pig embryos from 6 to 14 mm long, diverticula of the duodenum are found regularly. In slightly older pig embryos diverticula are found throughout the small intestine and occasionally in the cecum.

Cysts and diverticula of the intestines are in reality different phases of the same process. They result from the growth of a bud or from a prolongation of epithelium which has pushed out into the mesenchyme. The mesenchyme, as far as the intestine is concerned, consists of all the other layers of the intestine except the epithelial or mucosal lining.

After the bud has pushed its way into the mesenchyme it becomes vacuolated. If an opening into the intestine is effected, a diverticulum results, on the other hand, if the bud becomes separate, a cyst is formed. The walls of these cysts always contain the elements of intestinal structure.

In this connection, it is unwise to speak of true and false cysts as all are of similar origin, varying only in combinations of the different layers of the intestinal wall which enter into their formation.

It is possible that some cysts are formed in a different manner. To understand their origin better, one must for a moment revert to the embryologic development of the intestinal tube. In human embryos, Tandler found that a marked proliferation of the duodenal mucosa begins about the thirtieth day, resulting in complete occlusion of the intestine on the forty-fifth day. Then vacuoles begin to appear, and by the sixtieth day this lumen is again wide open.

The same process of epithelial proliferation and occlusion, with later canalization, occurs throughout the whole intestinal canal, but not with the great regularity seen in the duodenal segment.

Forssner maintained that congenital occlusions which persist are from mesoderm. Buds of mesoderm—*young valvulae conniventes*—push through the dense masses of epithelial cells which fill the lumen and meet similar buds from the opposite side. They coalesce, thus forming a bridge or septum. Caroway's case seems to show this clearly. In his case the lower end of the cecum, with the appendix opening into it, was completely shut off from the intestinal canal by such a septum.

Kreuter believes that such septums are formed from the epithelial elements, which become transformed into connective tissue.

The diagnosis of ileocecal cysts and cysts of the cecum is by no means easy. In most cases in which the diagnosis is made preoperatively, it can at best be only a shrewd guess. Even with the abdomen open, the exact nature of the condition cannot always be told. In some cases the final decision must await the microscope.

A movable tumor in the region of the cecum is suggestive. If the patient is a child the probability of ileocecal cyst is increased, although advanced age by no means excludes the condition.

A large percentage of the cases have shown symptoms of acute or recurring obstruction. In two of the cases reported in the literature, and in one of mine, intussusception existed concomitantly. Acute appendicitis has been the diagnosis in at least four of the cases reported. At operation the diagnosis can usually be made if a knowledge of this pathologic condition exists.

Both patient and surgeon will fare well if resection of the intestine is done. In no case has the attempt to enucleate the cyst been successful. I shall report three new cases.

REPORT OF CASES

CASE 1—A child, aged 9 months, was admitted to the hospital with symptoms of acute intestinal obstruction.

Physical examination showed a tumor somewhat larger than a hen's egg in the region of the cecum. It could be moved slightly from side to side and was not tender.

Operation—A right rectus incision revealed a tumor connected with the mesial wall of the cecum and the terminal ileum. The tumor was about 3 inches (7.6 cm) long and 1 inch (2.5 cm) by 1½ inches (3.77 cm) in cross-section. There were two grayish-white spots on the wall of the tumor. As the lumen of the cecum was encroached on greatly, it was decided that resection should be performed. Accordingly, about 2 inches (5 cm) of the terminal ileum, together with the cecum and appendix and 3 inches of the ascending colon, were removed, and side to side anastomosis was done.

The child recovered and was living and well two and a half years later. The child is now normal in all respects.

Pathologic Report (Dr. George S. Graham)—*Gross Description*. The specimen consisted of a segment of intestine 16.5 cm long (fig. 1). It consisted of terminal ileum with the ileocecal valve near one end and beyond it about 4 cm of cecum. Immediately above the junction of the small with the large intestine there was a protruding tumor mass 3 cm in diameter with a smooth serous-

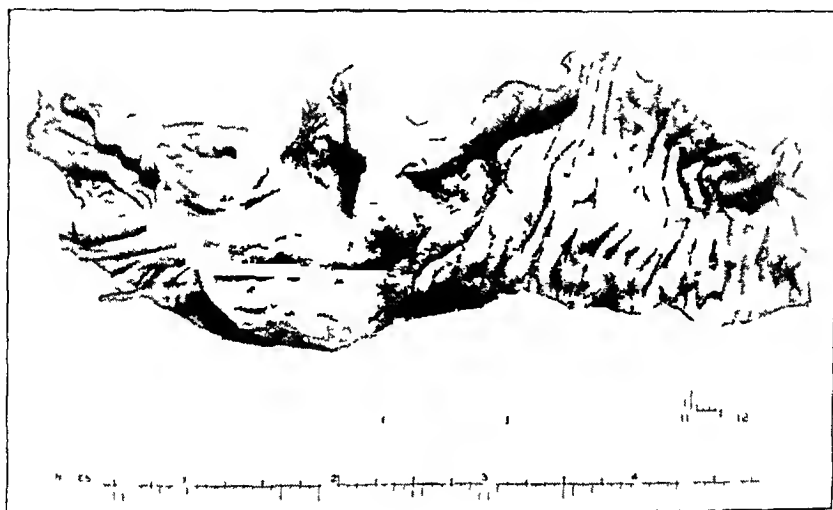


Fig. 1—Intramural cyst of the ileum. The cyst produces an inward bulging of the wall of the bowel, beginning just above the fold of the ileocecal valve at the left. Its cavity has been opened by transverse incision. A probe projects from the appendical opening.

covered surface. It had been opened by transverse incision, which revealed it as a cyst lying within the wall of the bowel. On the serosal side the wall of the cyst was dense, almost cartilaginous, and was from 0.4 to 0.6 cm thick. The muscular layer of the bowel could be followed into it. The inner wall or roof of the cavity was thinner but was also firm and appeared to contain smooth muscle. It was covered by the intestinal mucosa, beneath which the cyst bulged to form an elevation measuring 3.5 cm in the longitudinal axis of the bowel and 1.5 cm in the transverse axis. This elevation began just above the edge of the ileocecal valve. The cyst was lined by a smooth, dense, grayish-white tissue. In the mesenteric tissue were several lymph nodes, the largest being 1 cm in length. They were natural in color and consistence.

Microscopic Description. The cyst cavity was lined by a thin mucous membrane. This was best seen in blocks taken from the outer wall or the floor of the cavity (serosal side of the bowel) (fig. 2). Where best developed, it showed

a surface layer of high columnar cells dipping downward into short, wide crypts. Opening into these singly, or in groups of two or three, were short, wide, tubular glands lined by polygonal cells with clear vacuolated cytoplasm, like that typical

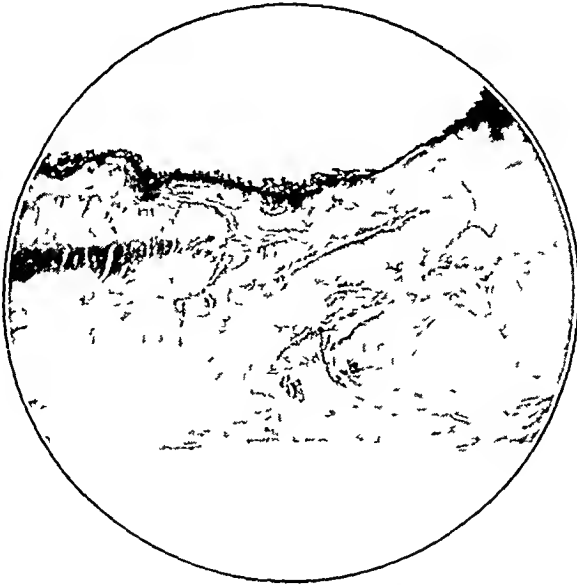


Fig 2—Outer wall or floor of the cyst, $\times 7$

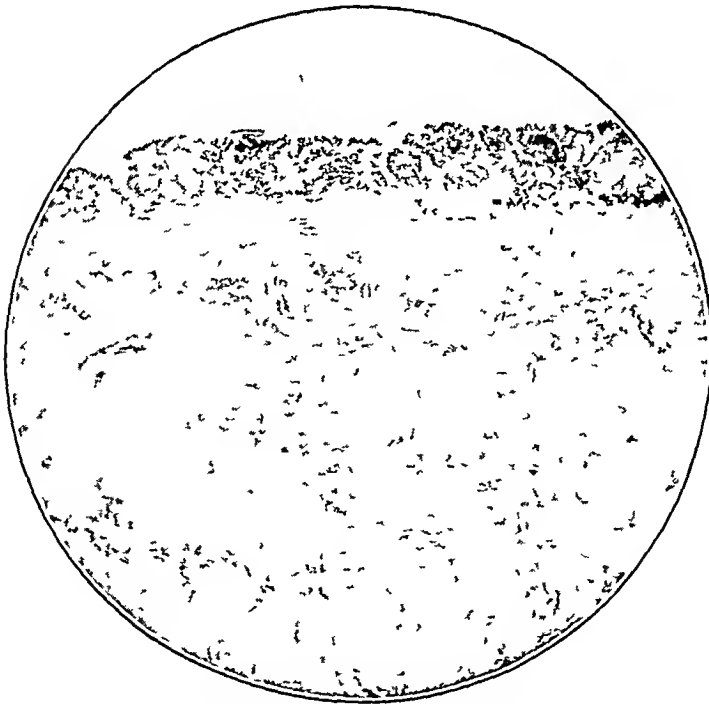


Fig 3—Outer wall or floor of the cyst, showing the mucosal lining, $\times 120$

of Brunner's glands (fig 3). The larger surface depressions often extended more deeply and subdivided the tissue into irregular papillary formations or outlined thinner villus-like structures. The tunica propria was relatively dense. In some blocks this atypical mucosa flattened into a single layer of columnar

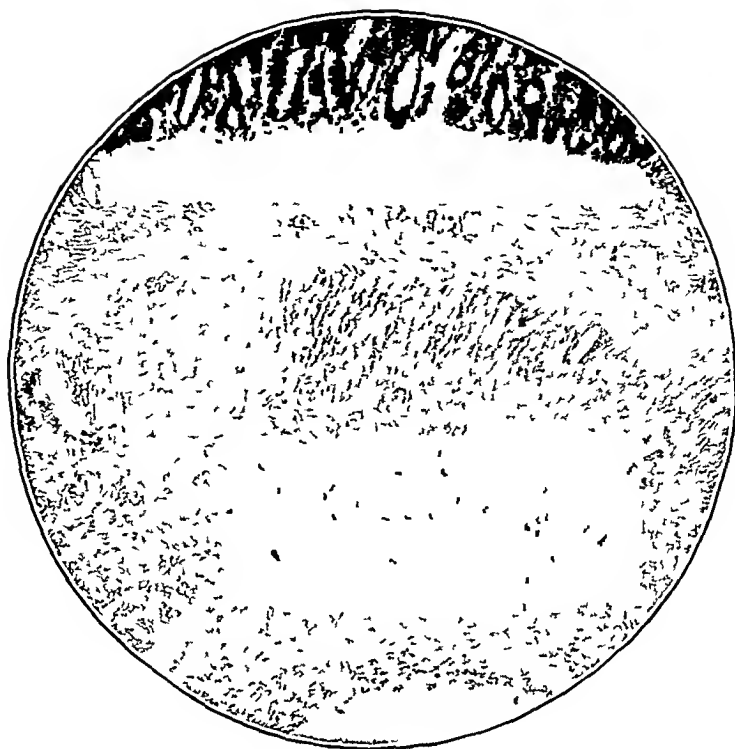


Fig 4—Inner wall or roof of the cyst. The lower level of the covering colonic mucosa can be seen at the top of the field. At the bottom is the denuded inner layer of the cyst cavity, $\times 120$

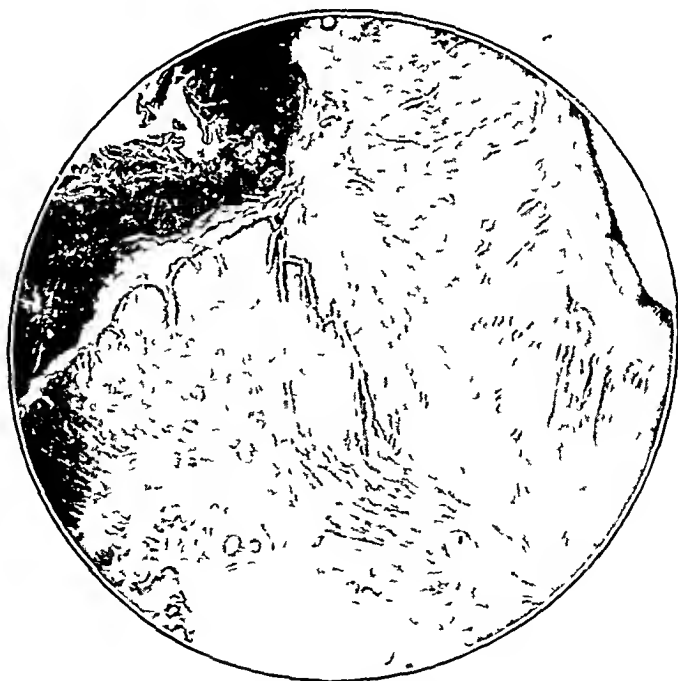


Fig 5—Angle of junction of wall of the bowel with the cyst. At the left is the uninvolved ileum, at the upper right, the cyst cavity, $\times 7$

epithelium with a thin supporting stroma and occasionally small sectors containing a few abortive glands. The flattening became more pronounced about the side walls of the cavity, and in the roof even this thinned mucosa disappeared, and the stroma was infiltrated by leukocytes. When present, the lining epithelium usually rested directly on a thick stratum of smooth muscle with irregularly disposed longitudinal and transverse strata, but this layer was absent in some sectors. Beneath it was a zone of connective tissue with infiltrating lymphocytes and eosinophils. Outside this there was a muscular wall of varying structure. In the floor it was thick and in general circularly disposed, but this thinned toward the roof where it was usually represented by two layers separated by a middle fibrous stratum (fig 4). In the angle in which the normal wall of the bowel met the cyst, its longitudinal layer was continued in the floor of the cyst. The circular layer appeared to split, sending a thick layer into the floor and the thinner bundles upward into the roof (fig 5). In both areas, the muscle bundles appeared to mingle with bundles proper to the wall of the cyst itself.

CASE 2—A child, aged 2 years, was admitted to the hospital with a history of vomiting and bloody stools of six days' duration.

A mass could be felt by rectal examination, and a tumor was palpable in the sigmoid region.

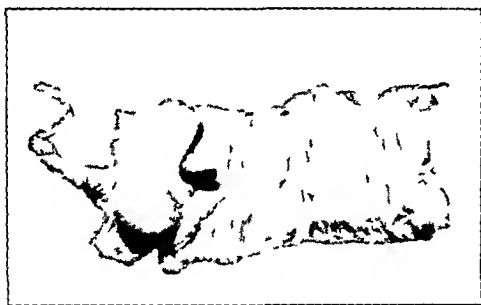


Figure 6

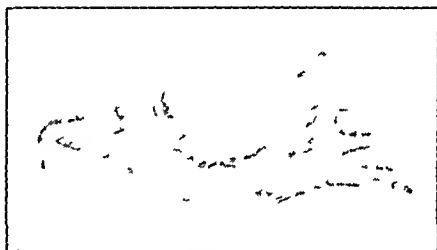


Figure 7

Fig 6—Intramural cyst of the ileum. The outline of the ileocecal valve fold is seen just to the right of the cyst. A probe has been passed into the lumen of the appendix and projects beneath the valve.

Fig 7—Section through the cyst in the transverse axis of the bowel. The "roof" is collapsed from shrinkage while in the preserving fluids, $\times 2$.

Operation—At operation a large intussusception was found. It was impossible to reduce the intussusception, as the ileum had sloughed in two places. Resection of all of the colon with its contained intussusceptum, leaving only the sigmoid, was done. The ileum was joined to the sigmoid by lateral anastomosis.

The patient died one hour later.

The cecum showed a small cyst on its posterior wall just above its ileocecal valve.

Pathologic Report (Dr George S. Graham)—*Gross Description*. The specimen consisted of a segment of bowel 85 cm long (fig 6). The vermiform appendix was attached near one end. On section the ileocecal valve was found near this end with the appendix opening beneath it. On the ileal surface of the valve there was a dome-shaped cyst 17 cm in diameter and 0.8 cm in height. The wall was thin, and the cavity contained a colorless fluid. The appendix emerged through the wall of the bowel just alongside and beneath the cyst.

Microscopic Description Sections showed an epithelial-lined cyst apparently lying within the inner muscular layer of the small intestine. The outer wall or floor of the cyst (the side toward the peritoneum) was lined by a mucous membrane containing simple tubular glands opening through relatively large pits. They were lined by high columnar cells with vacuolated cytoplasm. There were large vacuolations suggesting that of the "goblet cell" but no tinctorial suggestion of contained mucus. The short rounded or slightly elongated end-pieces were lined by an epithelium of similar appearance. The cells suggested those of Brunner's glands rather than those of the small intestine. There were no cells of Paneth. The tissue was best developed at one lateral angle of the floor of the cyst (fig 7) where it formed a thick layer with large and richly branching papillary folds. Outside this area it rapidly thinned into a single layer of columnar

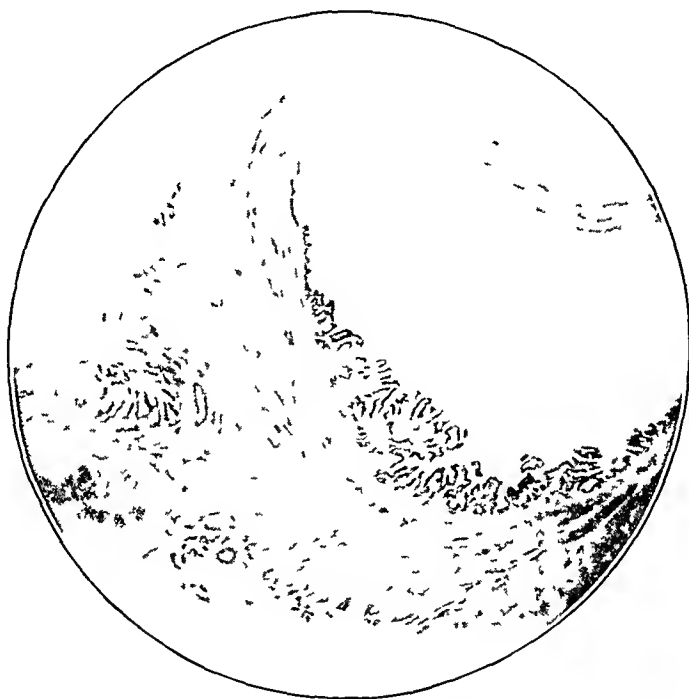


Fig 8—Higher power view, showing the junction of the ileal wall with the cyst, $\times 7$

cells. The tunica propria of the thicker area also thinned and disappeared, the epithelium resting directly on the smooth muscle of the wall. There was a discontinuous inner layer of smooth muscle, sometimes suggesting a muscularis mucosae but appearing for the most part merely as an inner layer of the enveloping tissue. As the muscular wall of the bowel met the cysts, its longitudinal muscle layer was continued in the outer wall or floor of the cyst. The circular layer appeared to split, sending a widened layer into the floor and a series of bundles upward about the sides of the cyst to its covering surface or roof (fig 8). The tissue of the latter was poorly preserved and its exact structure could not be clearly made out but it appeared to consist of a delicate fibrous tissue with an occasional trace of smooth muscle. It was covered in part by the intestinal mucosa but this had disappeared in large part and the inner or cyst surface was also denuded. Clinging to the inner wall of the cyst was a little serous or fibrinous coagulum with desquamated epithelial cells and a few leukocytes and red cells in its meshes.

CASE 3—In June, 1928, a woman, aged 21, was admitted to the hospital complaining of pain over the cecal region. There were tenderness and rigidity over McBurney's point. A diagnosis of acute appendicitis was made.

Operation—Operation was performed by Dr C N Carroway, of Birmingham, who permits me to report this case. At operation, a cyst was found occupying the lower end of the cecum; the appendix opened into the cyst. The caput cecum

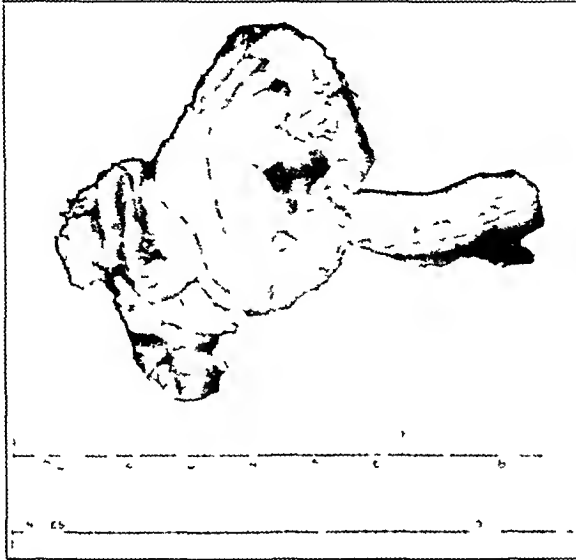


Fig 9—Cecal cyst. The appendix has been opened longitudinally. Its lumen opens into the cyst cavity, which also has been partially opened by incision through the roof.



Fig 10—Low power view of the cyst. The section passes tangentially through the orifice of the appendix, $\times 2$.

was excised, and the defect in the intestine was repaired by suturing cut edges together.

The patient made an uneventful recovery.

Pathologic Report (Dr George S. Graham)—Gross Description. The specimen consisted of the caput cecum (fig 9). There was a conical enlargement of its wall with the appendix coming off from its apex on the serosal side and its base bulging into the lumen of the bowel and apparently constituting a cyst wall. No appendiceal opening was present. The appendix was 4 cm long and was

slightly constricted at its cecal attachment. Incision through its distal portion showed a thickened dense wall and pus-filled lumen. A probe passed inward through the lumen entered the cavity of a cyst lying within the cecal wall and producing the deformity noted. It was filled with purulent fluid. It did not communicate with the lumen of the bowel. The muscular layer of the bowel appeared to cover the cyst on its serosal side, where it formed a thick dense wall. A thinner wall supported the colonic mucosa covering it on the side of the lumen of the bowel.

Microscopic Description Sections through the cyst showed that it was located within the mucous layer of the colon (fig 10). The muscular layers of the bowel lay in its outer wall or floor and were continued outward in the appendix.

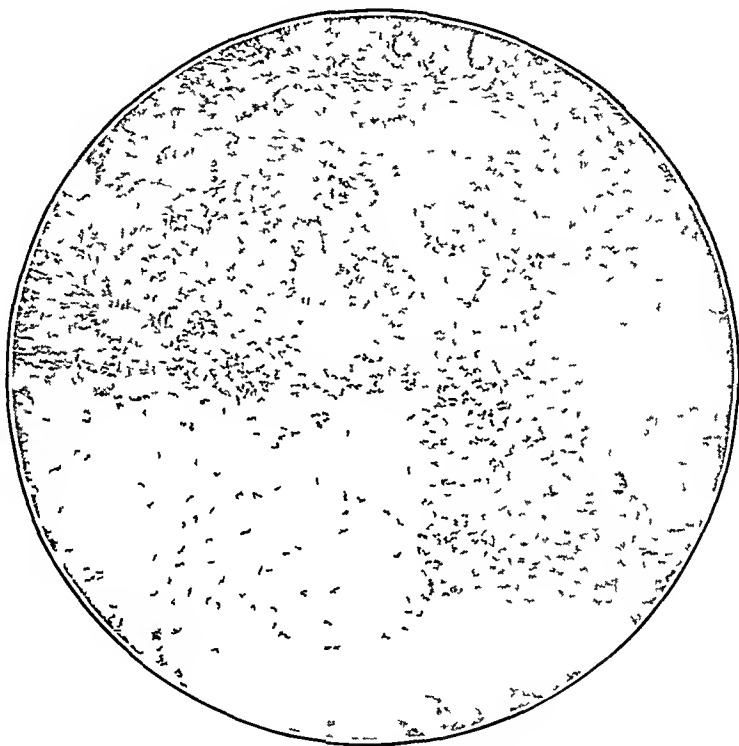


Fig 11—Roof of the cyst. The lower margin of the covering mucosa can be seen at the top, the cyst cavity is just within the field at the bottom. There is inflammatory exudate in the whole thickness of the wall, $\times 120$.

where this structure communicated with the cyst cavity. The roof of the cavity consists of colonic mucosa supported on a layer of loose fibrous tissue containing occasional fat cells and continuous with the submucosa of the enveloping wall of the bowel (fig 11). Immediately about the appendical orifice the inner surface of the cyst cavity was lined by typical colonic mucosa (fig 12). Elsewhere no trace of mucosa was found, the inner loose fibrous tissue of the wall being infiltrated by great numbers of leukocytes and in places broken up by miliary abscesses (fig 13). The leukocytes were mostly neutrophils, but there were occasional lymphocytes and plasma cells, endothelial leukocytes and in places many eosinophils. The inflammatory exudate spread laterally in the mucosa of the colon about the cyst and outward in the muscularis and serosa of the floor of the cyst. There was slighter extension outward in the proximal appendix, but the mucosa of the latter was well preserved.



Fig 12—Junction of the appendix with the cyst cavity The section passes tangentially to the lumen at its upper end, $\times 7$

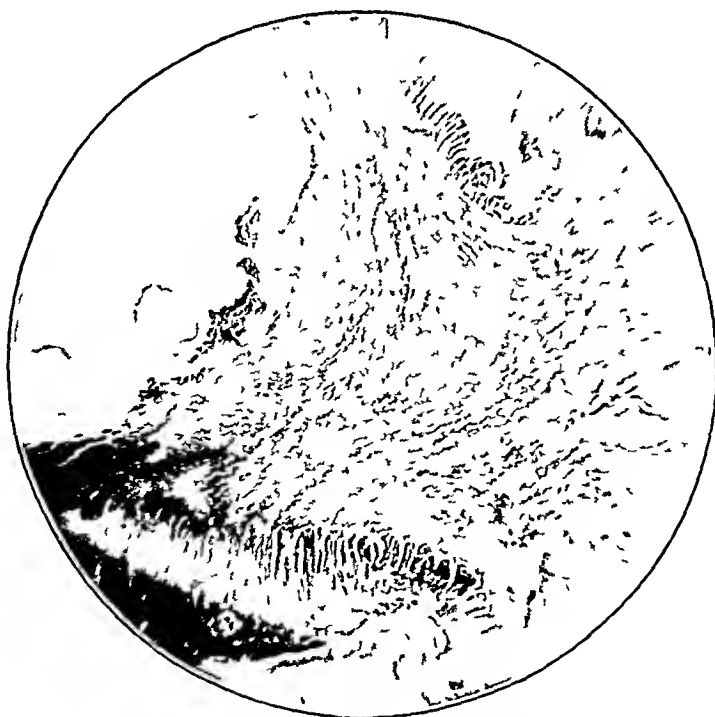


Fig 13—Lateral wall of the cyst The colonic mucosa is reflected over its roof at the upper left, the muscular coat of the bowel passes to the left in the floor of the cyst, $\times 7$

REVIEW OF VERIFIED CASES IN THE LITERATURE

In 1882 Frankel¹ reported the first case of ileocecal cyst to be found in the literature. A child died three days after birth, with symptoms of intestinal obstruction. At autopsy a cyst $2\frac{1}{2}$ inches (6.27 cm) in diameter was found at the ileocecal junction. It projected into the ileum and the cecum. No microscopic examination was done, but the age of the child and the observations at autopsy are undoubted evidence that this was a genuine ileocecal cyst.

In 1886 Sainsbury² reported the case of a girl, aged 11, who had died of typhoid. At autopsy a large cyst was found in the cecum just above the ileocecal valve.

In 1896 Hueter³ reported a cyst the size of a cherry stone situated at the ileocecal valve. It was covered only by mucosa.

The case Sprengel⁴ recorded in 1900 occurred in a girl, aged 15 years. A laparotomy was done for suspected tuberculous peritonitis. The cecum was resected for tumor. A cyst $1\frac{1}{4}$ inches (3.14 cm) long was near the ileocecal valve in the cecum. It was covered by serosa, and did not communicate with the lumen of the intestine. Microscopic examination showed columnar epithelium, tubular glands, lymphoid tissue and a few muscle fibers.

In 1902 Hedinger⁵ described a case in a boy, aged 4. The cyst was very large and occupied a large part of the lower part of the abdomen. It contained a liter of milky fluid. It was attached to the mesentery of the ileum 10 cm from the ileocecal valve. Section showed a peritoneal coat, two muscular coats, muscularis mucosae and an epithelial lining. The lining showed cylindrical epithelium and flattened epithelium for the most part, and in some places epithelium was missing.

In 1903 Krogius⁶ reported a case in a child, aged 2 months. The diagnosis was intestinal obstruction. At operation, a cystic tumor the size of a pigeon's egg was found in the ileum near the cecum, ileostomy was performed. A few days later excision of the intestines was done but the child died of hemorrhage two hours after the operation. While no microscopic observations are given, Krogius reported it as an enterogenous cyst which it probably was.

In 1906 Ayer⁷ reported a case in a man, aged 23, who was operated on for a condition supposed to be appendicitis, accompanied with severe

1 Frankel. *Virchows Arch f path Anat* **87** 275, 1882.

2 Sainsbury. *Tr Path Soc* **38** 146, 1886-1887.

3 Hueter. *Beitr z path Anat u z allg Path* **19** 391, 1896.

4 Sprengel. *Verhandl d deutsch Gesellsch f Chir* **29** 105 (pt 1) and 537 (pt II), 1900.

5 Hedinger. *Virchows Arch f path Anat* **168** 146 1902.

6 Krogius. *Ztschr f klin Med* **49** 53, 1903.

7 Ayer. *Am J M Sc* **131** 89, 1906.

pain, vomiting and constipation. It was found, however, that the condition present was a thick-walled cyst, the size of a duck's egg. Here, as often occurs in these cases, even with the abdomen opened, the diagnosis was doubtful. The case was at first considered one of intussusception. However, the cecum was incised, and a cyst was found overhanging the ileocecal valve. No microscopic examination was made, but the thick-walled cyst was apparently lined with mucous membrane.

In 1910 Neupert⁸ reported the case of a boy, aged 10, with a painful tumor in the ileocecal region.

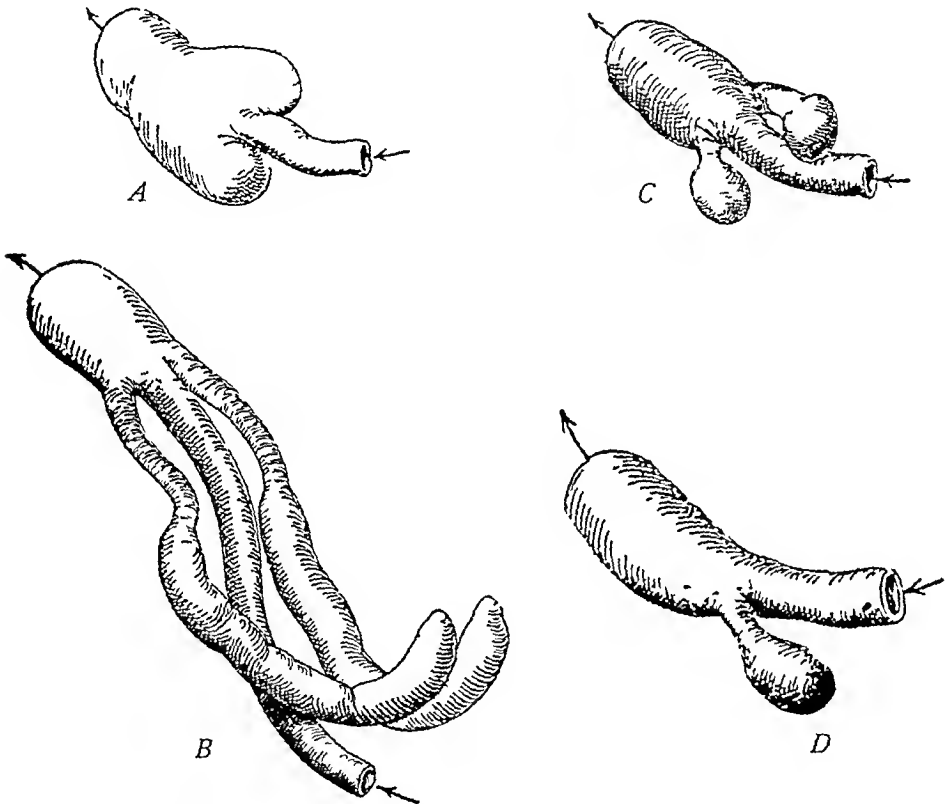


Fig 14—Types of ileocecal region (from Kelly: *The Vermiform Appendix*, 1905). A, two cecal pouches. American manatee, armadillo and many carnivorous birds. B, long cecal pouches of herbivorous birds (long narrow neck and small orifices). Goose, hen, owl, loon, ostrich, etc. C, short cecal pouches, narrow neck. Little anteater. D, prolonged pouch and reduction in caliber in mole and spiny anteater.

At operation a tumor the size of a hen's egg was found in the terminal ileum, 4 inches (10.16 cm) from the ileocecal valve. The cyst was enclosed on all sides by muscularis of the intestines and was lined by cubical epithelium with traces of mucosa.

⁸ Neupert. *Centralblatt für Chirurgie* 37:714, 1910.

In 1912 Baldwin⁹ reported a case of true diverticulum of the cecum, with a history of appendicitis-like attacks which had occurred twelve and 7 years previously. A hard globular tumor 2 inches in diameter was found springing from the cecum at the ileocecal valve. It contained hard feces and communicated with the cecum by an opening which just admitted the tip of the finger. There was no pedicle, but a clamp was applied next to the cecum and the tumor cut away. On microscopic examination it was found that the wall of the tumor contained all the coats of the normal cecum. The patient recovered.

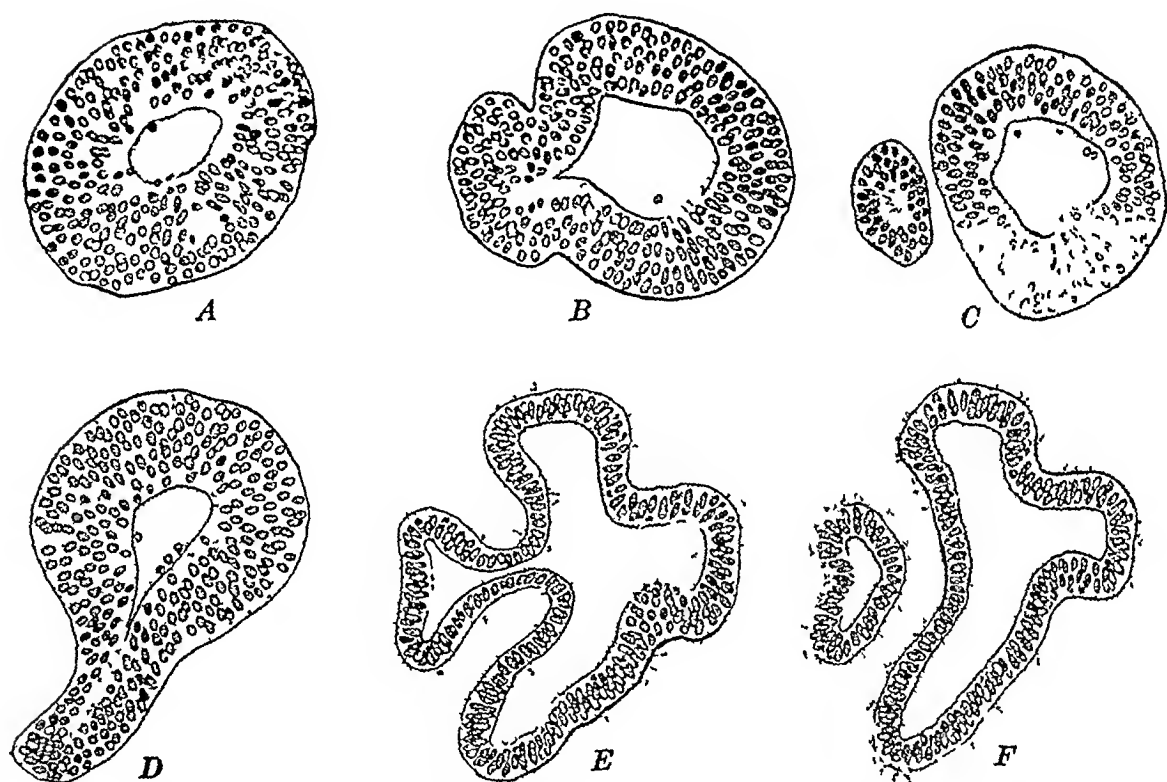


Fig 15—Cross-sections of the epithelial tube of the intestine, showing the development of diverticula, $\times 130$. A-D, from an embryo of 228 mm (Harvard Collection, Series 871). E and F, from an embryo of 30 mm (Harvard Collection, Series 913). (After Krebel and Mall. Human Embryology, 1912, vol 2, p 381.)

In 1913 Blackadder¹⁰ reported a case which was described as a retention cyst of the cecum. It occurred in an infant, aged 10 weeks. The tumor projected into the cecal lumen. Section showed a cyst covered with mucous membrane similar to that of the intestine. It was lined with a thin layer of columnar epithelium, which was folded in places and showed gland formation. Beneath the epithelium was a distinct submucosa then three distinct layers of muscular fibers. It was undoubtedly an enterogenous cyst.

⁹ Baldwin. M. Rec. **81** 991, 1912.

¹⁰ Blackadder. Tr. Am. Pediat. Soc. **25** 296, 1913.

Turner and Tipping,¹¹ in 1914, described a case in a child, aged 4 months. At operation, a cyst 1 inch (2.5 cm) in diameter was found encroaching on the lumen of both the ileum and the cecum. Its wall contained the coats of the normal intestine.

In 1914 Ball¹² reported a case in a child, aged 3 months. At operation the condition was thought to be an irreducible intussusception. Resection was carried out, when the colon was incised, a tensely distended cyst was seen to project from the wall of the cecum, blocking the ileocecal valve.

Bolton and Lawrence,¹³ in 1916, reported a case in a child aged 3 months. The cyst was in the mesentery at the ileocecal angle. It seemed to be incorporated with the wall of the cecum and the terminal ileum. It was incised, and glairy white, odorless fluid escaped. The greater part of the wall of the cyst was cut away. After prolonged drainage of similar fluid, the wound closed. Later, incision was required on two occasions to liberate a similar collection of fluid from the cavity.

In 1923 MacAuley¹⁴ reported a case in a girl aged 6 months. After the intussusception was reduced a tumor could be palpated at the ileocecal valve. Resection was performed.

In 1925 Bazin¹⁵ reported a case of intussusception in a boy aged 8 months. After the intussusception was reduced, a hard mass was found on the mesial wall of the cecum just above the ileocecal valve. The lumen of the cecum was encroached on. The cecum was resected. The child lived. Microscopic examination showed that the outer wall contained mucosa, submucosa and two muscular layers, all comparable to that of the adjoining cecum. It was lined by a thin layer of cuboidal cells.

In 1925 Lotheissen¹⁶ reported a case in a woman aged 21. He found a large cyst in the interior of the cecum. He resected the ileocecal region, after failing to enucleate the cyst.

In 1928 Edwards¹⁷ operated on a girl aged 12, who was thought to have acute appendicitis. A cyst 3½ inches (8.87 cm) long and about 1½ inches (3.77 cm) in diameter was in the right wall of the cecum, just above the ileocecal valve. It contained the structures of the wall of the intestine.

11 Turner and Tipping. *Proc Roy Soc Med* 7 29, 1913-1914.

12 Ball. *Brit J Dis Child* 2 259, 1914.

13 Bolton, C., and Lawrence, T. W. P. *Brit M J* 2 248, 1916.

14 MacAuley, H. F. *Brit J Surg* 11 122, 1923.

15 Bazin, A. T. *Canad M A J* 15 130, 1925.

16 Lotheissen. *Deutsche Ztschr f Chr* 179 394, 1923.

17 Edwards, Harold. *Clin I* 57 319 (July 4) 1928.

In 1929 Evans¹⁸ reported a case in a man, aged 29, who was operated on for a variable tumor in the cecal region. At times a distinct tumor could be felt, and again no sign of it could be found. It contained milky mucoid fluid. The walls of the cyst contained all the elements of the cecal wall, of which the cyst was really a part.

Resection was carried out with prompt recovery.

Evans also reported a case found in a specimen in the Royal College of Surgeons Museum (specimen no 1221 1). It consisted of "a spherical retroperitoneal cyst 4 inches in diameter, intimately connected with the lower end of the ascending colon.

"Histologically the wall of the cyst consists of fibrous tissue with intermingled unstriated muscle fibres, lined with well developed mucus secreting epithelium. Here and there the surface raised into low papillae."

In 1929 Beekman¹⁹ reported a case in a girl aged 5½ years. A diagnosis of partial intestinal obstruction was made, the possibility of intussusception being kept in mind. At operation, a cyst about 1½ inches in diameter was found encroaching on the ileum and cecum and connected with the mesial cecal wall. It contained a thick, glaucous, yellowish, mucoid fluid. The edges of the cyst were sewn to the parietal peritoneum. A fecal fistula developed. This was closed by a second operation seven months later. The child has since remained well.

CONCLUSIONS

Cysts of the ileocecal region constitute a definite entity.

They are enterogenous developmental cysts. True diverticula of this region have the same origin.

Malignancy has not been noted in connection with these cysts.

Three of the twenty-three cases have been associated with ileocecal intussusception.

Resection of the terminal ileum and cecum is the surgical procedure of choice.

Dr. George S. Graham supplied the pictures for these case reports.

18 Evans, A. *Brit J Surg* **17** 34 (July) 1929.

19 Beekman. *Ann Surg* **90** 1097 (Dec) 1929.

THE CLOSED METHOD OF TREATMENT OF FRACTURES OF THE ANKLE JOINT

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MILAN, ITALY

My object in this paper is to report the methods and discuss the results obtained in the closed reduction of recent fractures of the ankle joint at the surgical clinic of the University of Milan

The choice of methods to be employed in the treatment of these fractures is still a matter of discussion Lambotte,¹ Lane,² Leclerc,³ Alglave,⁴ Berard, Picot,⁵ Duval,⁶ Basset,⁷ and Juvara advocated operative reduction in the fracture with marked displacement, for the following reasons (1) A better reduction can be obtained and the fragments are maintained in better apposition, (2) the time required for union is less, and (3) function is more quickly reestablished

Guillembot, Tuffier, Delbet,⁸ Lusena, Matti,⁹ Lussana,¹⁰ Leveut, Girode, Monard and Monod prefer, as a rule, closed reduction They expressed the belief, however, that operative reduction is not infrequently indicated, as, for instance, in those cases in which there is multidirectional displacement of the foot, when there is a large anterior or

* Submitted for publication, March 14, 1930

1 Lambotte, Abbin *Chirurgie opératoire des fractures*, Paris, Masson & Cie, 1913

2 Lane, W A *Les conséquences désastreuses de certaines fractures par abduction du cou-de-pied*, *Lancet* **2** 697, 1921

3 Leclerc, G *Le traitement des fractures de Dupuytren par le vissage de la malleole interne*, *Bull et mem Soc de chir de Paris* **48** 1267, 1922

4 Alglave, P *Au sujet de la technique du traitement sanglant des fractures bimalleolaires a grand déplacement*, *Bull et mem Soc de chir de Paris* **50** 152, 1924

5 Picot, G *L'intervention sanglante dans les fractures malleolaires*, *J de chir* **21** 529, 1923

6 Duval, Pierre, and Basset *Indication et technique du traitement opératoire des fractures récentes fermées du cou-de-pied*, *Bull et mem Soc de chir de Paris* **49** 1415, 1923

7 Basset, A *Fracture récente du cou-de-pied double fragment marginal postérieur ostéosynthèse par vissage excellent résultat anatomique et fonctionnel*, *Bull et mem Soc de chir de Paris*, 1924 vol 50

8 Delbert, P *Deux cas de fracture de Dupuytren* *Bull et mem Soc nat de chir de Paris* **48** 421, 1922

9 Matti *Die Knochenbrüche und ihre Behandlung* Berlin Julius Springer 1922

10 Lussana *Le fratture del collo del piede* *Arch ital di ortop* **42** 155 1926

posterior fragment of the tibia with a tendency for the foot to become dislocated again after it has been reduced, when the fractured malleolus and astragalus infringe on the remaining portion of the fractured internal malleolus, reduction thus being prevented, and, lastly, when the malleolar fragments become crossed and locked so that the foot remains in the abducted position

Baldo Rossi,¹¹ Savariaud,¹² Soligoux,¹³ Feriy and Delbet expressed the belief that reduction can be accomplished and maintained by the closed method in every type of fracture through the ankle joint, however complex. They also were of the opinion that the results obtained by the closed method equal or surpass those obtained by the operative method. I recently had the opportunity of examining patients who had been treated for fractures through the ankle joint at the Surgical Clinic of Milan, and found that in 435 cases of this character it had not been necessary to resort to an operation, even in the more serious and complex cases with pluridirectional displacement of fragments.

The external displacement of the foot is the most difficult to correct. The valgus position of the foot occurs when the astragalus is no longer held in position as a result of a fracture or diastasis of the malleoli. The external dislocation of the foot must be completely corrected, otherwise, there will be complex dynamic and static changes in the mechanism of the ankle joint which is under great strain, even under physiologic conditions. If, in addition to the valgus position, a backward dislocation of the foot occurs as a result of a fracture of the posterior margin of the articular surface of the tibia, difficulties in treatment are increased. A perfect anatomic reconstruction must be secured before a good functional result can be obtained. At times good reduction can be secured, at other times reduction is difficult, even under anesthesia and with the aid of the x-rays because of (1) the amount of displacement, (2) the peculiar shape of the fragments, and (3) the relation of the soft tissues to the fragments. Many surgeons, especially the French, are inclined to treat these fractures by the open method, not only to secure a reduction of the fragments but also to maintain reduction by fixing by nail or screw the external malleolus to the tibia, or by fixing the posterior marginal fragment to the tibia (Lane, Lambotte and others).

There is no doubt that good results may be obtained by these procedures, but we think that as good, if not better, results can be obtained

11 Rossi, Baldo. Lussazioni associate a frattura e fratture associate a lussazione, Comunicazione al XVII Congresso di Ortopedia, Venezia, 1926.

12 Savariaud. L'appareillage des fractures bimalleolaires recentes, en adduction forcee constitue la procede de choix il doit être prefere a la methode sanglante, *Presse med* **32** 377, 1924.

13 Soligoux. À propos du fragment marginal posterieur dans la luxation du pied en arriere, *Bull et mem Soc de chir de Paris* **38** 1470, 1912.

in most cases without operation. I believe that I am correct in saying that the closed method is to be preferred in the treatment of these fractures. Infection with serious consequences is the chief danger of the open operation. Stiffness of the joint will result if infection occurs. Delayed bony union, as the result of the use of foreign material and the intolerance of the tissues to it, must be considered as a distinct disadvantage of the open reduction of these fractures.

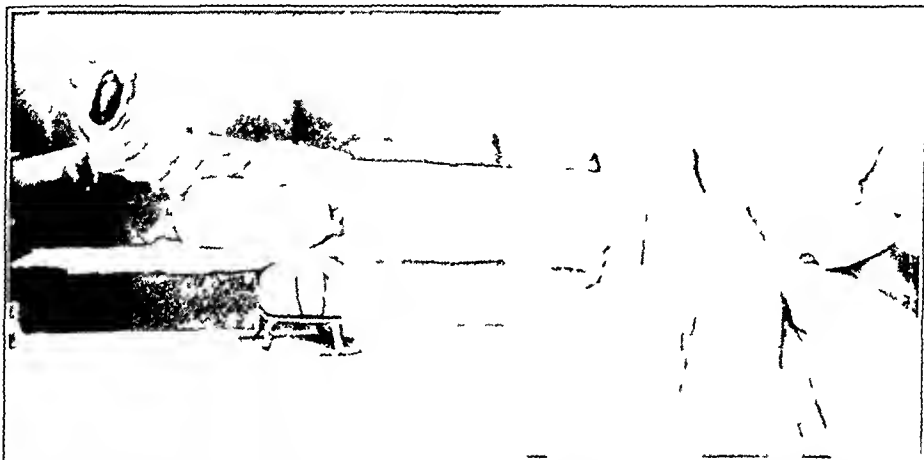


Fig 1—Construction of the temporary internal splint apparatus, showing arrangement of the cotton wool cushion between the splint and the lower third of the leg



Fig 2—Showing the way to wrap the linen bandages in the construction of the internal splint apparatus in order to place the foot in the varus position

When the closed method is employed it is not good practice to apply a circular cast or to use even the Delbet dressing when the reduction is first made because the reduction when first attempted may be difficult and incomplete, and again the dressing must be padded with absorbent cotton because of the possibility of reactive and circulatory changes occurring about the fracture. Plaster loses a considerable part of its

fixation power when padded with absorbent cotton. Complete or partial recurrence of the displacement may occur as soon as the swelling is reduced and the dressing becomes loose.

When plaster is used there may be some difficulties in the reduction of fractures with marked and combined displacements, especially displacements lateralward and posteriorly. It is difficult to maintain

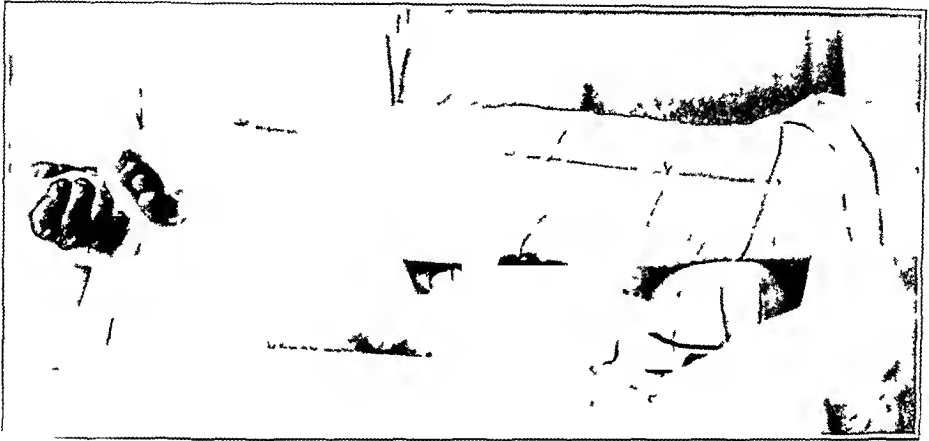


Fig 3—Degree of final varus of the foot obtained with the internal splint. It is to be noted that the plantar surface of the foot is turned directly to the inner side.

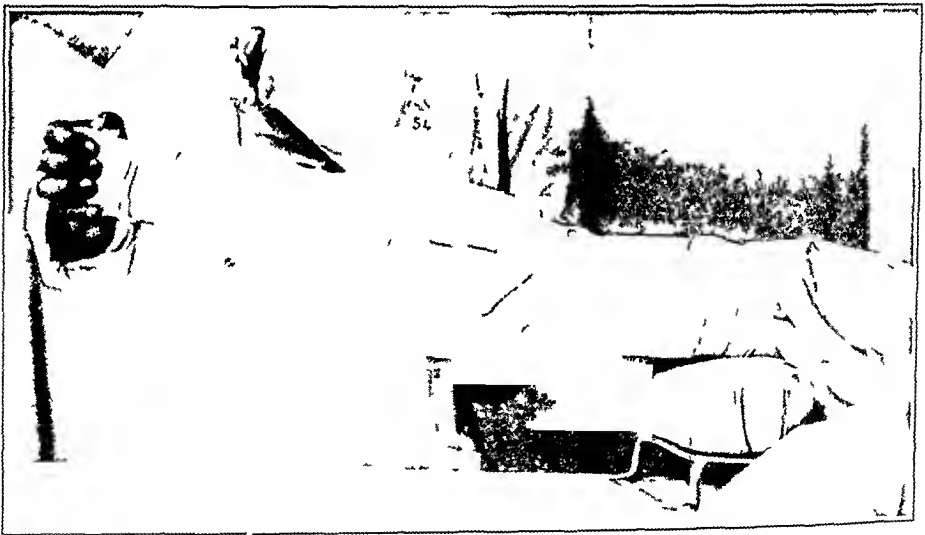


Fig 4—At the end of the construction of the internal splint apparatus the foot must be at right angle with the leg. This position may better be maintained by a traction plaster of paris stirrup.

reduction during the time required for the setting of the plaster. All the force used in the reduction will not be transferred to the foot by the plaster. For example, in the treatment of fractures of the neck of the femur, if the plaster used sets, a great part of the result of traction is lost when traction is released. In some fractures of the malleoli with

marked lateral displacement, in order to overcome the tibiofibular diastasis, to secure a good reduction of the fragments and to prevent a recurrence of the valgus position, it is necessary that the reduction be maintained by a force as powerful as that used in the reduction.

This is accomplished by a lever, to be described later, by which the fracture is reduced and reduction maintained. Even if all the force required could be secured by a circular plaster cast to maintain the foot in an overcorrected position, this would be undesirable because of the pressure that might develop with the subsequent edema and the consequent possibilities of gangrene. Sometimes one must be satisfied

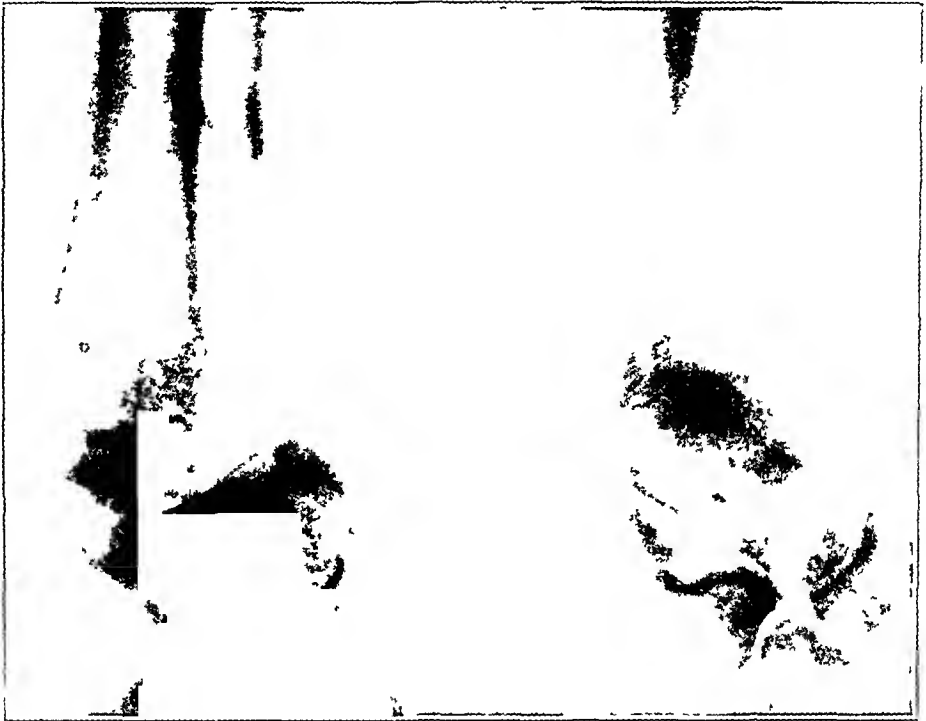


Fig. 5—Roentgenogram of a typical Dupuytren's fracture with marked tibiofibular diastasis in G. P., aged 49, valgus position and subtotal posterior luxation of the astragalus.

with incomplete reductions imperfectly maintained by padded dressings which do not maintain in good position the more marked displacements which tend to recur. In such cases one may at times be almost ready to admit that open reduction has certain advantages.

The temporary lever apparatus used by Professor Baldo Rossi in the Surgical Clinic of Milan for the reduction of the lateral and posterior displacements of the foot is the Dupuytren apparatus to which has been added some important modifications which make it more efficient. After the temporary reduction by this apparatus plaster is used for immobilization.

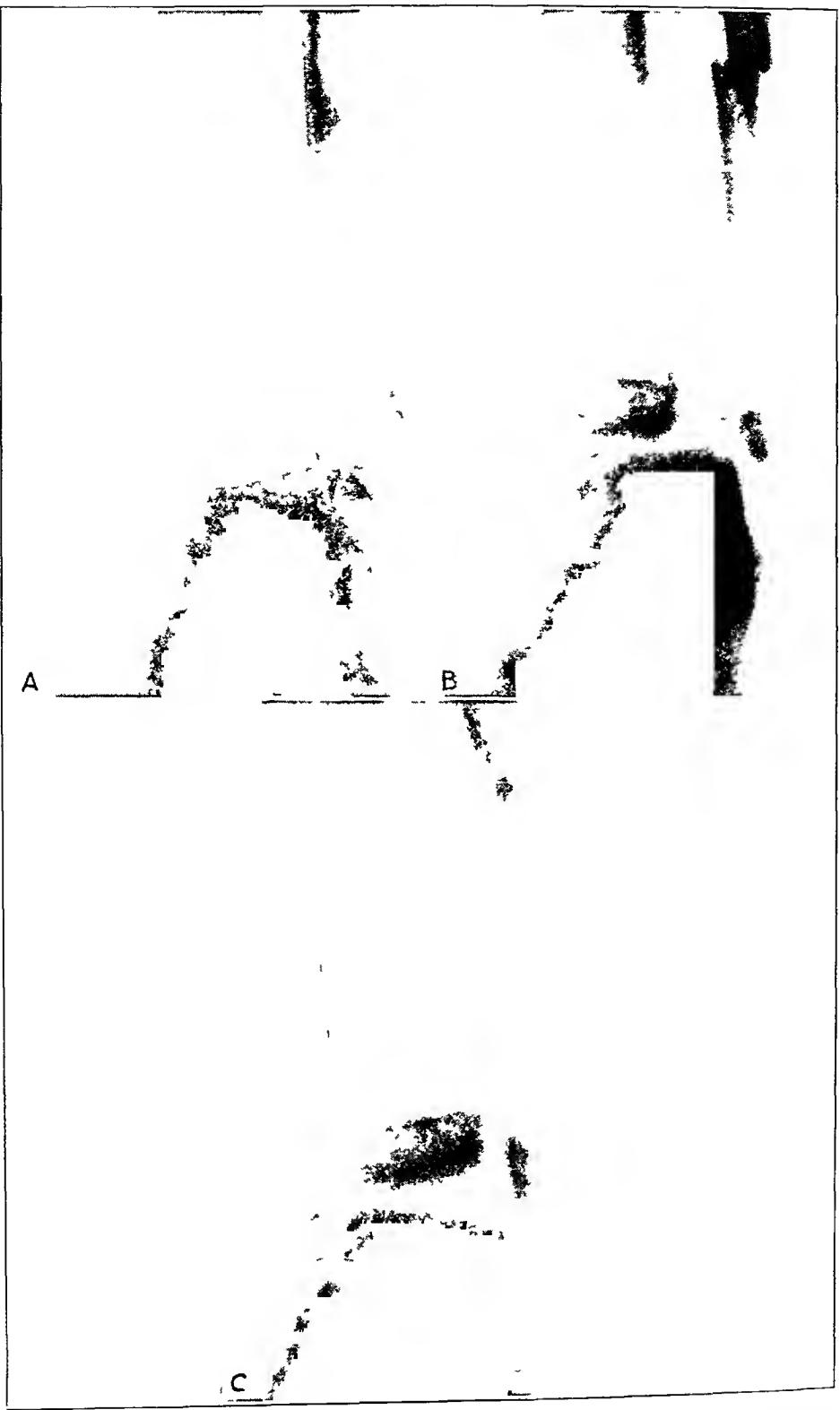


Fig 6—Roentgenograms of the same patient as in figure 5. *A* shows the first step of the reduction with the internal splint apparatus. The reduction is not complete. *B* shows the second step of the reduction with the internal splint apparatus. Although improved, the reduction is still incomplete. In *C*, the reduction of all the displacements (of the diastasis, of the internal malleolus and of the astragalus) is completed at the third applications of the internal splint apparatus.

A description of this apparatus and the way that it is used follows

1 The lower extremity is covered with a layer of absorbent cotton. A wooden splint (from 90 to 100 cm long, 6 cm wide and 1 cm thick) also covered with absorbent cotton is placed on the inner side of the extremity. It extends from the distal two thirds of the thigh distalward to 10 cm beyond the plantar surface of the foot.

2 A large pad of cotton is now placed between the inner surface of the lower two thirds of the leg and the splint. The thickness of this pad must be proportionate to the degree of the varus position which it is desired to obtain.

3 The upper part of the splint is fixed by means of bandages which below include the cotton pad. There must be considerable space between the foot and the splint. This is secured by the cotton pad.

4 After manual correction of the gross displacement, the foot is forced, by means of bandages, tighter and tighter against and over the inferior third of the splint, so that the foot is in a marked varus position. In this way, the lateral displacement is corrected.

It is not always easy to secure the varus position at once. The reduction is secured by degrees by tightening of the bandages and corrective maneuvers about the heel. It would not be wise—frequently it is impossible—to secure by a single violent manipulation a complete reduction of the fragments in some of these cases. Occasionally the fracture cannot be reduced. This happens with other procedures especially in attempts at manual reduction, reduction not being maintained when the plaster is applied. The operator may tire and therefore attempts to reduce the fracture more quickly, employing sudden and violent manipulations, which are interrupted. Muscular contractures, especially when the patient is not asleep (hence the frequent necessity of administering an anesthetic in this procedure), interfere greatly with the reduction.

The method advocated in this paper permits of gradual and progressive reduction. The muscle spasm is overcome gradually, and the traumatized tissues gradually accommodate themselves. The pain which the patient suffers is limited in intensity. Except in rare cases an anesthetic is not required.

The bandage should be applied so that the roll when tightened causes a gradual reduction of the fracture with the foot in an overcorrected position. The bandage should be applied from without inward so that the foot is brought into the proper position as indicated in figure 2. Several rolls of the bandage should be tightly applied so that the reduction secured may be maintained. The foot must be kept at right angles or almost at right angles, for this position is most favorable for the reestablishment of function especially so when there is a possibility of some stiffness of the ankle joint after immobilization.



Fig 7—Roentgenograms (*A* and *B*) of a low Dupuytran fracture (instead of the fracture of the internal malleolus there is a tear of the internal lateral ligament), a posterior marginal fracture, valgus position, diastasis of the tibio-fibular joint and external subluxation of the astragalus, in M G, aged 51
C shows complete correction of every displacement with internal splint apparatus

5 If in addition to the eversion there is also a posterior dislocation of the foot, this must be corrected before the foot is brought into the varus position by bandaging it to the internal splint. Cases in which the dislocation is combined with a large posterior marginal fragment of the lower end of the tibia must be differentiated from those in which the posterior dislocation is the result of a marked diastasis of the tibia and fibula. In the cases of the first group pressure of the foot directed from behind forward must be maintained while the foot is brought pro-

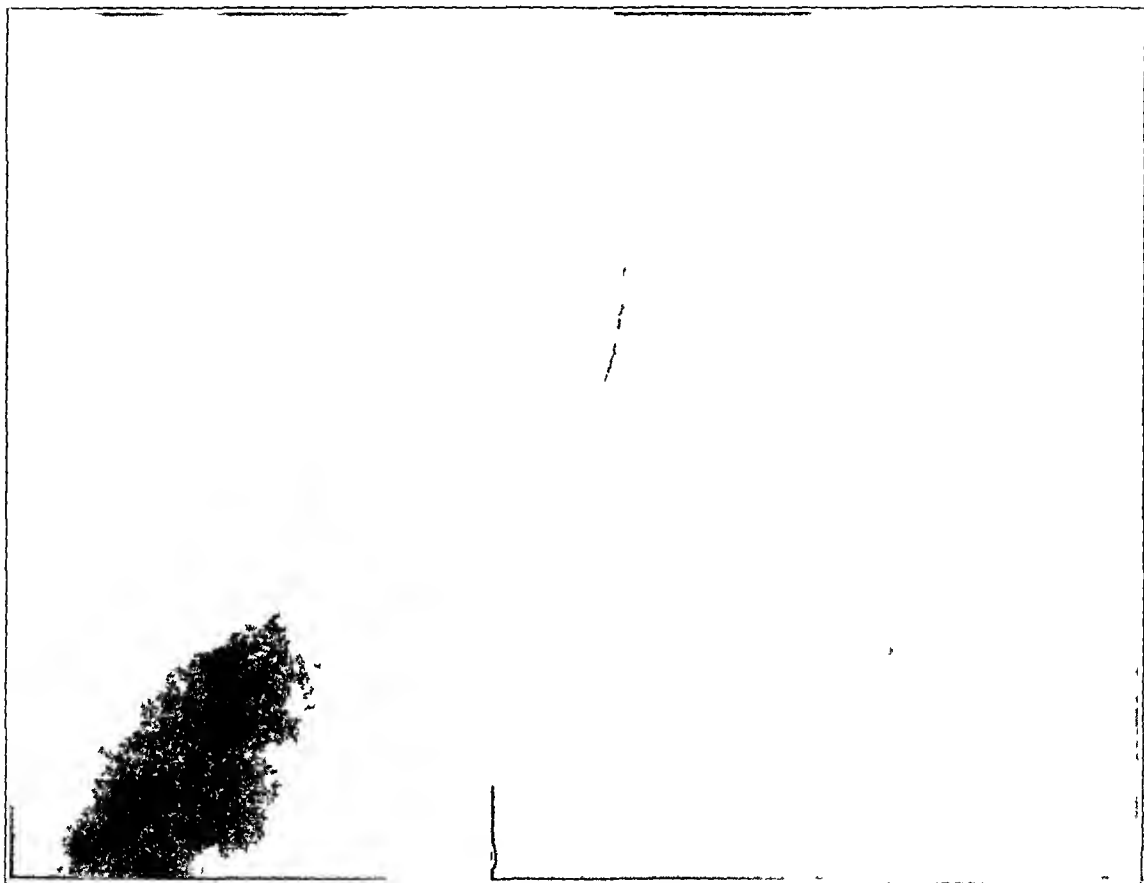


Fig 8—Roentgenograms showing a low Dupuytren's fracture and posterior marginal fracture of the tibia with diastasis, valgus position and posterior dislocation of the foot, in G. G., aged 37

gressively into the overcorrected varus position, the foot being kept at a right angle. Such a procedure prevents recurrence of the posterior dislocation and also reduces the posterior marginal fragment. The dorsal capsular ligament of the tibia tarsal articulation is made tense and the fragment is brought downward and forward until it is contacted with the fractured surface of the tibia. In the second group of cases in which the dislocation is dependent on the wide diastasis of the tibia and fibula, reduction is made more easily if before the foot is brought

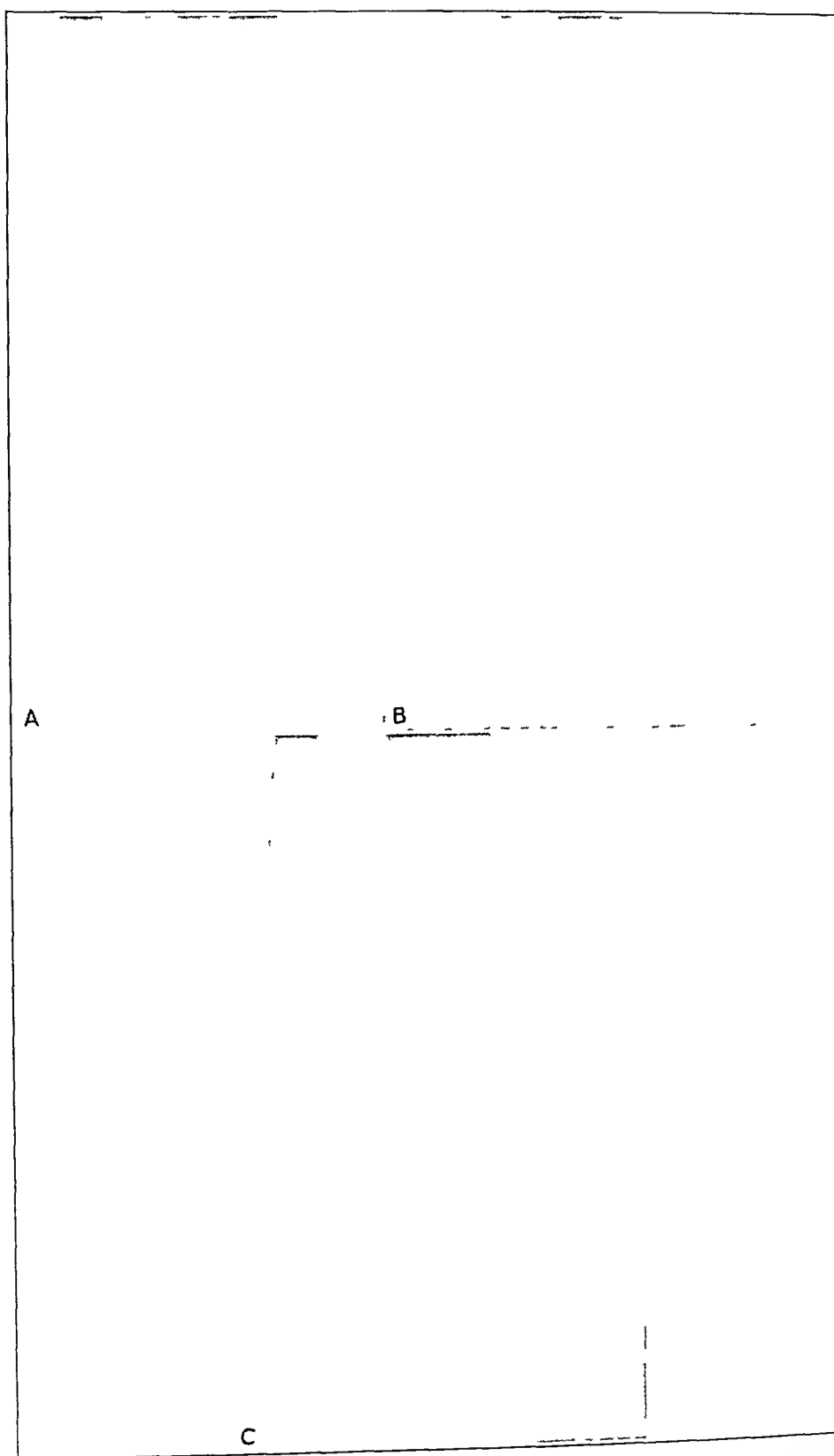


Fig 9—Roentgenograms of the same patient shown in figure 8. In *A* and *B*, with the first temporary internal splint apparatus, the posterior luxation of the foot has been reduced, while a light degree of tibiofibular diastasis still persists. In *C*, at a second application of the internal splint apparatus, the complete reduction of every displacement is obtained.

forward the valgus position is temporarily exaggerated so that the astragalus passes more easily over the posterior border of the articular surface of the tibia. When reduction occurs there is a characteristic jerk. Reduction may be maintained without any special precaution while the bandage is applied about the foot and splint.

6 When reduction is completed a roentgenogram must be taken at once in two planes in order to determine whether or not the results are satisfactory. If the correction is not satisfactory the astragalus, although in supination not bearing the proper relations to the articular

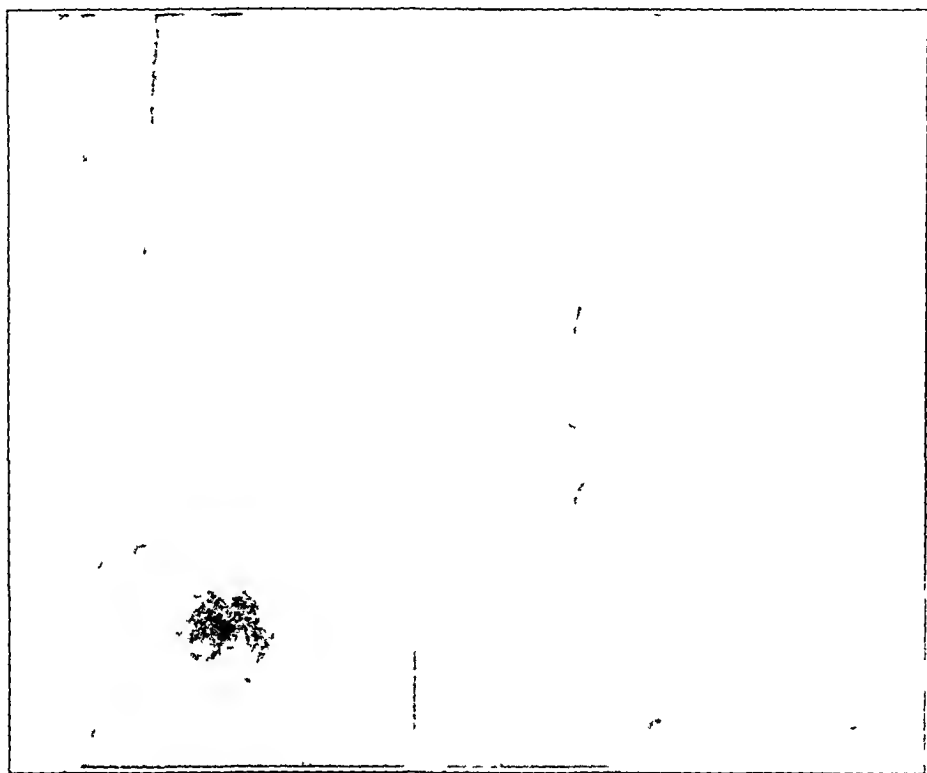


Fig. 10—Roentgenograms showing good anatomic and functional result in G. G., after seven months.

surface of the tibia or the lower fibular fragment not being placed in its proper relation to the tibia, attempts can be made deliberately to improve the results preferably on the following day. The cotton pad used is replaced by a larger one, and the bandage is again applied as already indicated. There is no great hurry, for one of the advantages of this dressing is that the reduction may be made by degrees without traumatism of the tissues for the muscular resistance is gradually overcome.

7 The temporary internal splint is left in position from eight to twenty days, depending on whether there is swelling of the soft tissues, the amount and complexity of the displacement and the time required in the different stages of reduction.

As a rule, if good reduction has been secured there is no necessity of changing the apparatus. If there is marked swelling of the tissues or abrasions and wounds of the skin which require attention, it will be well to reapply the dressing which may become loose as the edema subsides.

The application of this dressing is not difficult or complicated. No special equipment is required. Reduction can be secured even when there is not complete muscular relaxation at first and when there are those bony displacements which many regard as making the fracture irreducible. The reduction is made by a powerful lever of the second

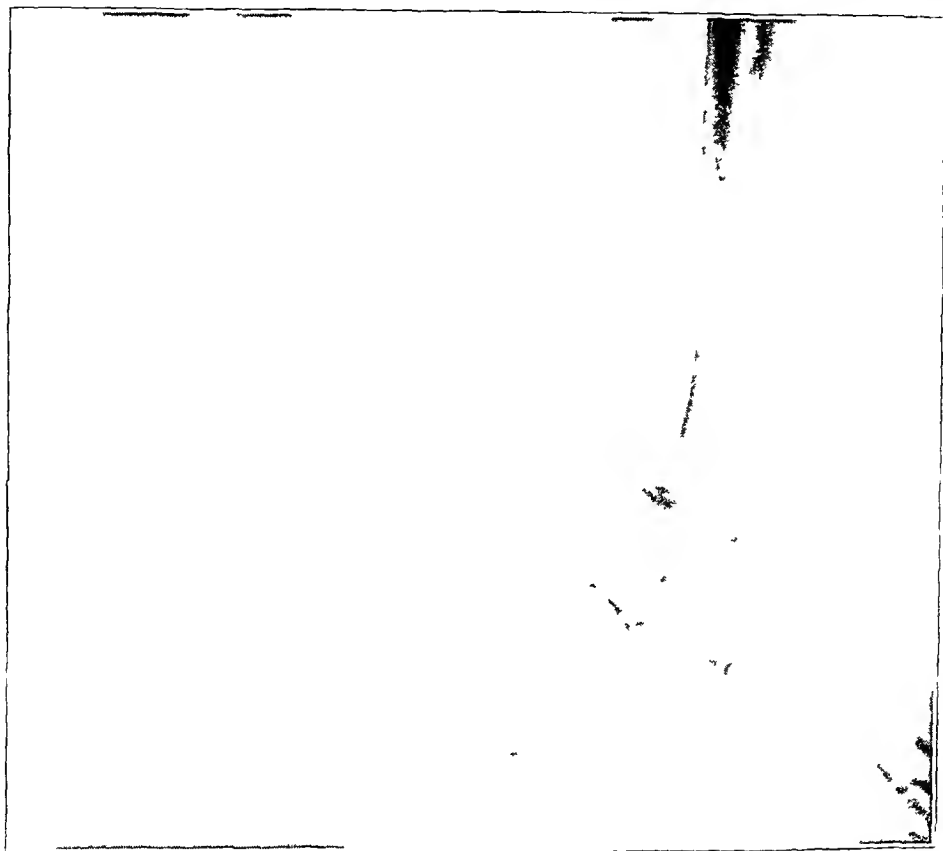


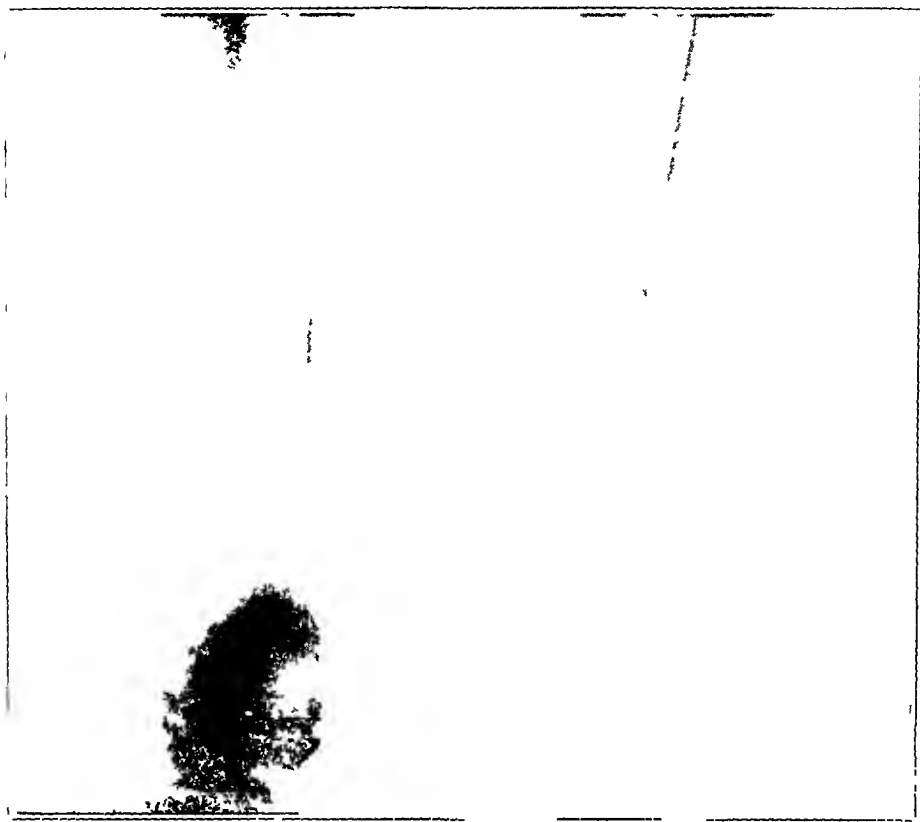
Fig. 11—Roentgenograms showing internal malleolar fracture by adduction with a large fragment and posterior marginal fracture tibia with slight varus position and complete posterior dislocation of the astragalus and of the foot, in C. T., aged 19.

class, the fulcrum of which is formed by the cotton pad and force of which is produced by the tight bandage over the foot. The resistance is represented by the distal part of the splint. This is a lever with a continuous, progressive, graduated force.

When it is thought that a satisfactory reduction has been secured this original dressing is removed and a circular plaster cast applied in order to maintain the reduction effectively. The plaster cast is applied over a stockinet fashioned to fit the leg and foot, so that the plaster will

be accurately adapted to the parts. A strip of cotton may be used over each malleolus to prevent pressure and over the upper and lower ends of the cast so that cutting of the skin will be prevented. If the cast is so applied, the displacements will not recur. The redisplacement of the posterior marginal fragment has been noted most frequently. The recurrence of this displacement has been regarded by some surgeons as a justification and indication for the open operation.

I believe that these recurrent displacements are due to the too early use of plaster before the edema has subsided and to employment of



12 Roentgenograms of C T, showing complete and perfect reduction of every displacement in the temporary internal splint apparatus

absorbent cotton beneath the plaster cast, especially if it is circular, which does not permit of firm fixation about the malleolar and dorsal surface of the foot, particularly if the tissues are swollen and edematous when the cast is applied.

The temporary internal splint maintains reduction even when the edema decreases, for it is more than a fixation apparatus, it acts as a lever which continues to act even after the displacement has been reduced. Although the cotton padding and the disappearance of the edema may lessen the power primarily exerted, this lever exerts enough

force which continues to act as long as the splint is left in position to maintain reduction

The plaster cast extends as high as the tuberosities of the tibia as a rule, motion at the knee being permitted. In cases of more marked and serious displacements, the cast embraces the lower third of the thigh. If there has been a marked displacement of the fragments, it is advisable to take a roentgenogram even after the plaster has been applied to determine whether the reduction is satisfactory.

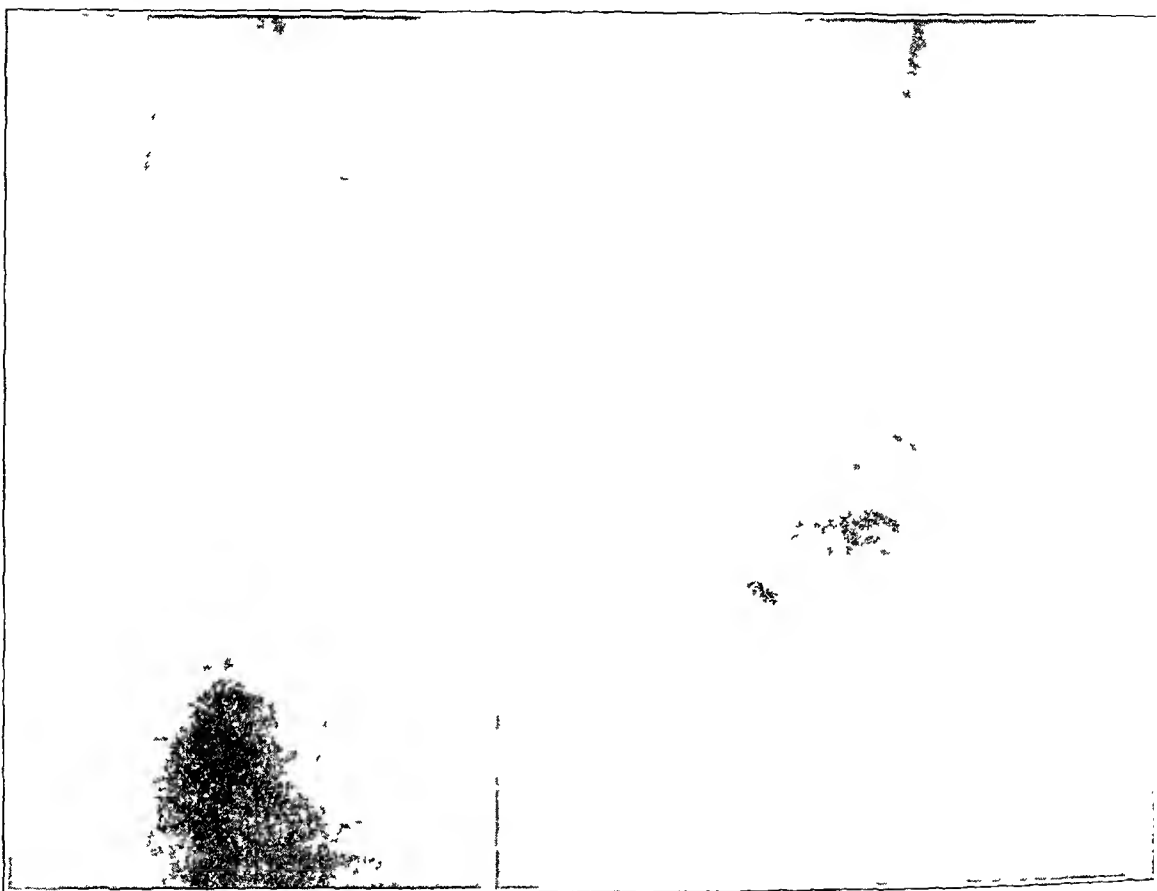


Fig. 13—Roentgenograms showing subtotal separation of the lower epiphysis of the tibia with separation of a posterior cuneiform metaphyseal fragment and with supermalleolar fracture of the fibula, posterior and external deviation of the axis of the leg, in D. B. C., aged 15.

I prefer the circular cast to Hergott's so-called plaster gutter, the plaster splints of Maissonneuve and the apparatus suggested by Reclus and Delbet. A plaster cast applied from eight to ten days after a fracture carries no dangers and maintains reduction. Almost immediate, even if partial, use of the fractural limb is permitted. No further observation is required, and the patient can be dismissed the day after it is applied.

The cast is left on for thirty, sixty or seventy days, depending on the type of fracture. The cast must not be removed too early, and the formation of callus in malleolar fractures is frequently delayed. In order to secure good bony union, immobilization must be continued for more than two months. After such long immobilization the stiffness of the joint which may develop is of no marked significance, for it usually disappears in one or two weeks when physiotherapy or rational treatment is instituted.

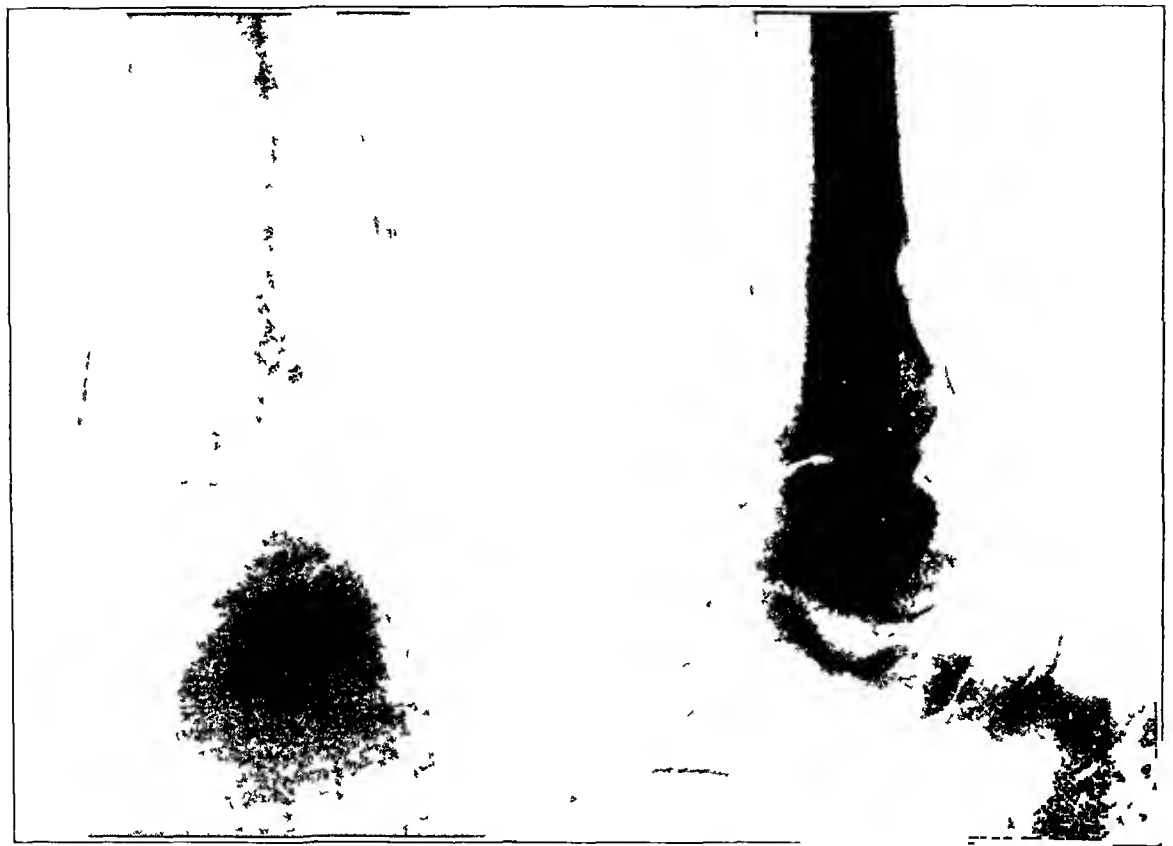


Fig. 14—Roentgenograms of D, B, C taken after four years, showing good anatomic and very good functional result.

When the cast is removed, an examination is made to determine whether or not there is good union. A roentgenogram should be made to determine the amount of callus formation. One can then judge whether or not it is best to permit of weight-bearing on the fractured leg. If movements of the foot and weight-bearing cause pain, and if the roentgenogram reveals fibrous callus insufficiently consolidated, a lighter cast is applied after gentle massage and passive motion of the foot has been instituted. This second cast may be worn twenty, thirty or forty days, depending on the case.

When the cast is finally removed, the after-treatment is begun, massage, hot baths, diathermy and artificial sun baths are employed to promote the circulation, reduce the edema and hasten the formation of bony callus and union.

Some of the results of this method of treatment are indicated in the figures appearing in the body of the article.

This method of overcoming the valgus position by use of the internal splint can also be used in supramalleolar fractures, and in epiphyseal separations with or without a fracture of the metaphysis of the tibia when in the valgus position.

In conclusion, I believe that the closed treatment of fractures of the ankle joint, if properly employed, satisfies all the surgical indications.

His statement applies to the more serious malleolar fractures with the original fragment of the lower end of the tibia and to those with multidirectional displacements of the astragalus and of the foot. I believe this the method of choice in the treatment of these fractures, but do not deny that cases may be met in which an operation must be performed because the fragments cannot be reduced in any other way. In 435 consecutive fractures of this type observed by me no operation has been required.

THE REGENERATION OF HYALINE CARTILAGE IN JOINTS

AN EXPERIMENTAL STUDY *

A R SHANDS, JR, M D
DURHAM, N C

Before the work of Redfern¹ in 1851, it was thought that hyaline cartilage possessed little or no power of regeneration. Since that time the experimental studies on hyaline cartilage have shown that it possesses this property, but the investigators cannot agree as to the exact method by which it is brought about. The object of this communication is to review the more significant papers in the literature on the regeneration of hyaline cartilage in joints, ribs and ears, and to present the results of experiments on the injury and healing of hyaline cartilage in the joints of dogs. The literature of this country contains no experimental reports of such work in joints. Most of the reports have come from England, Germany, France and Italy.

Hunter² published an article, "The Structure and Disease of Articulating Cartilage," in which he said, "From Hippocrates to the present age it is universally allowed that ulcerated cartilage is a troublesome thing and that when once destroyed it is not repaired." It was in this article that the *circulus articuli vasculosus*, or the vascular border of the joint, was first described. Leidy,³ following a series of experiments on cartilage, concluded that after the rupture of articular cartilage the fragments never unite. Kolliker⁴ wrote that cartilage possessed no power of regeneration, nor did wounds of cartilage heal by a proliferation of the cartilage substance. In the same year, Paget⁵ stated that there were no instances in which a lost portion of cartilage had been

* Submitted for publication, Feb 7, 1930

² From the Surgical Hunterian Laboratory of the Johns Hopkins University Medical School, Baltimore

1 Redfern, Peter. On the Healing of Wounds in Articular Cartilage, *Month J M Sc* **13** 201, 1851

2 Hunter, William. On the Structure and Diseases of Articulating Cartilage, *Philosophical Tr Roy Soc*, London **9** 267, 1743

3 Leidy, Joseph. On the Intimate Structure and History of the Articular Cartilage, *Am J M Sc* **17** 277 (April) 1849

4 Kolliker, A. Manual of Human Histology, London, Sydenham Society, 1853, vol 1, p 59

5 Paget, James. Healing of Cartilage, Lectures on Surgical Pathology, London, Longman (and others), 1853, vol 1, p 263

restored or a wounded portion repaired with new and well formed cartilage, and that the gap of cartilage in a fracture into a joint became filled with tough fibrous tissue

Since 1850, a great many investigators have contributed a wealth of material to the subject of the regeneration of hyaline cartilage in joints. The best piece of experimental work in the early period was that of Redfern⁶. He showed that wounds in articular cartilages healed perfectly by the formation of fibrous tissue at the site of the injury. This fibrous cicatrix, he found, consisted of white and of yellow fibers, which were formed from the intracellular substances of the cartilage and from the nuclei of its cells, respectively. He observed that the cartilage cells lying near the cut surface might be enlarged and rounded or oblong in shape, that they were filled with corpuscles, and that occasionally they projected into the mass on the cut surface. These cells were in a position to discharge their contents whenever the cell wall should offer too little resistance to the escape of the contents. The stimulus of the incision was thought to have produced an abnormal development of the cells of the part through which it had passed. Redfern⁶ demonstrated that after injury a fibrocellular layer was formed from the increased proliferation of cartilage cells, with an accompanying softening and fibrillation of the hyaline substance. This layer was firm enough to be torn off with its nipple-like processes from the cartilage, and not infrequently formed a permanent fibrous cicatrix.

Gurlt⁷ concluded that the loss of cartilage substance could be repaired through fibrous tissue, which was sometimes like cartilage, but never fully cartilaginous tissue. The fibrous tissue was found to change itself by degrees into connective tissue cartilage and fibrocartilage. Gussenbauer⁸ made the statement that wounds of the cartilage in which the bone was not broken did not heal.

Ogston⁹ wrote of the focus of central growth in cartilage. He believed that the cartilage grew toward the joint surface, as well as toward the joint, from this central focus. This was in order to replace the loss of cartilage from the forces acting on the surface and to replace the cartilage surface toward the joint, which was being constantly

6 Redfern, Peter. Observations on the Development and Nutrition of Bone and Cartilage and on the Relations of the Connective Tissues to Each Other in Health and Disease, *J Anat & Physiol* 32 96, 1897-1908

7 Gurlt, E. F. Beiträge zur vergleichenden pathologischen Anatomie der Gelenkkrankheiten, Berlin, 1853

8 Gussenbauer, Carl. Ueber die Heilung per primam Intentionem, *Arch f klin Chir*, 1871, vol 12

9 Ogston, Alexander. On Articular Cartilage, *J Anat & Physiol* 10 49, 1875-1876

worn away Ogston¹⁰ further stated that articular cartilage was as valuable and necessary in forming and maintaining the structure and shape of bone as was the periosteum The cartilage, however, unlike the periosteum could not in a short space of time proliferate laterally, but grew only toward the epiphysis, and if a portion was removed in making a perforation, the adjacent portions could not proliferate toward or into the perforation

Tizzoni¹¹ reported that in cartilage covered with perichondrium the restoration of the cartilaginous tissue began in the perichondrium In further experiments with joint cartilage, he found that on the edge of the incision the cartilage cells had become smaller and showed granular degeneration, while in the adjoining layers of cartilage the cells showed enlargement He also observed fibrin formation in the matrix between the superficial and the adjoining layers of cartilage, which later was changed into cartilaginous tissue He found that in incisions through the cartilage to the subchondral bone, there was a metaplasia of the fibroblasts of the marrow into new cartilage cells

Prudden¹² described the changes that took place in the proliferation of the cartilage cells There was found to be an increase in the bulk of the fibers of the intranuclear network and occasionally a definite grouping of these fibers into more or less conical-rayed figures at the opposite poles of the nuclei The newly formed nuclei were sometimes enclosed in the body of the cell, but in many cases were seen lying completely outside of the latter and pressed closely against the capsule In many cases, there was a distinct new formation of separate cells within the enlarged cavity, in others, there seemed to be simply a multiplication of the nuclei but no differentiation into separate cell bodies When completely developed cells were formed, they were in no case separated by the formation of a partition of basement substance across the cavity, such as is seen in the proliferation of cartilage cells under normal conditions He further observed that the absorption of the cartilage took place by cells growing in from the surrounding granulation tissue

Gies,¹³ in studying the healing of joint wounds in cartilage, showed that an aseptic wound of cartilage did not heal, but that an infected wound with maceration healed completely He also observed that after trauma, there was an extensive degeneration of hyaline cartilage

10 Ogston, Alexander On the Growth and Maintenance of the Articular Ends of Bones, *J Anat & Physiol* **12** 503, 1878

11 Tizzoni, Guido *Arch per le sc med* **2** 28, 1878

12 Prudden, T M Experimental Studies on the Transplantation of Cartilage, *Am J M Sc* **82** 360, 1881

13 Gies, T Histological and Experimental Study of Joint Disease IV The Healing of Wounds in Cartilage, *Deutsche Ztschr f Chir* **18** 8, 1882

Seggel¹⁴ observed that after four days the young capsule forms of cartilage cells adjacent to the defect sometimes became decidedly enlarged and later formed mitoses. He demonstrated that after twelve days islands of loose cartilage in a defect started to become changed into connective tissue and took part in the formation of the scar. It was shown that cartilage reacted to trauma with proliferation of cartilage cells showing mitoses and formation of new hyaline matrix. These areas were always well circumscribed. Seggel further found that in an intact linear incision of cartilage after five months there was no reaction and that a superficial and central defect of cartilage remained more or less the same in this time.

Fasoli¹⁵ found that after forty-six days there was protrusion of proliferated cartilage from the cartilage incision, and that after twenty weeks there was a complete repair of cartilage which had been cut through to the bone. Rimann¹⁶ described a metaplastic cartilage formation in the deep defects in cartilage with no change along the edges of the cartilage. He showed that after thirty-one days the defect became filled with cellular connective tissue from the marrow, which was changed into cartilage. Ciociola¹⁷ demonstrated that wounds of cartilage extending to the underlying bone presented a definite transition from connective tissue to hyaline cartilage, and that the tangentially placed superficial wounds which did not reach the bone showed scarcely any reaction after two months.

Fisher¹⁸ contradicted Ogston's idea of a focus of central growth and stated that the superficial cartilage cells had the same function as the perichondrial cells of the lateral part of the articular cartilage, and were the parent cells of the more fully developed cartilage cells in the deeper parts. He also demonstrated that the repair near the margins of the articulating cartilage was good, but that nearer the center it was poor unless the underlying cancellous bone had been exposed. Fisher further showed that after six weeks the pared off cartilage from the condyle of the femur showed no sign of repair on the pared surface, but that the cartilage in the lateral part did show proliferation.

14 Seggel, Rudolf. Experimentelle Beiträge zur Anatomie und Pathologie des Gelenkknorpels. II. Studien über Knorpelwunden und Defekte, *Deutsche Ztschr. f. Chir.* **75** 453, 1904.

15 Fasoli, G. Sul comportamento delle cartilagini nelle ferite, *Arch. per le sc. med.* **29** 365, 1905.

16 Rimann, Hans. Experimenteller Beitrag zur Lehre von der Entstehung der echten, freien Gelenkknorpel, *Virchows Arch. f. path. Anat.* **180** 446, 1905.

17 Ciociola, F. Contributo allo studio della riparazione delle ferite delle cartilagini articolari, *Polichinico (sez. chir.)* **28** 229 (June) 1921.

18 Fisher, A. G. T. A Contribution to the Pathology and Etiology of Osteoarthritis, with Observations upon the Principles Underlying Its Surgical Treatment, *Brit. J. Surg.* **10** 52, 1922-1923.

Ito,¹⁹ experimenting with rats, proved that the defect in articular cartilage was first filled with granulation tissue which became fibrous and then was changed into fibrocartilaginous tissue, and finally into cartilage. In some of his experiments, it was demonstrated that the reparative tissue came from the underlying cancellous tissue, while in others transitional cartilage-like tissue seemed to arise in connection with the edges of the synovial membrane. Fibrous tissue was demonstrated filling the defect in one week, a transitional tissue between fibrous tissue and cartilage in two weeks, and islets of new cartilage in fibrous tissue in three weeks.

Haebler,²⁰ experimenting with the articular cartilage of dogs, found that when the cartilage alone was injured without injury to the subchondral bone, the cartilage wound showed no change after 300 days. This proved to him that the cartilage itself possessed no power of regeneration. When the subchondral bone was injured, as well as the cartilage, the cartilage defect became filled with fibrous tissue.

A great many of the experimental studies on the regeneration of hyaline cartilage have been with cartilage completely enveloped with a perichondrium, such as that found in the ribs and ears. Marchand²¹ after experiments with costal cartilage concluded that cartilage wounds were healed by the proliferation of a layer of connective tissue from the perichondrium, which became partly changed into fibrocartilage. He found that the defect was first filled with fibrin. In about two weeks the cartilage itself showed little change, but there was a thickening of the perichondrium. After four weeks there was a moderate fibrous thickening and a new formation of the hyaline cartilage tissue, which came from the perichondrium.

Matsuoka²² and Mori,²³ both experimenting with cartilage of the ear in rabbits, confirmed the conclusion of Marchand. Malatesta,²⁴ experimenting with the costal cartilage of rabbits, stated that only exceptionally can the cartilage and connective tissue surrounding the

19 Ito, L. K. The Nutrition of Articular Cartilage and Its Method of Repair, *Brit J Surg* **12** 31, 1924-1925.

20 Haebler, C. Experimental Study of the Regeneration of Joint Cartilage, *Beitr z klin Chir* **134** 602, 1925.

21 Marchand, F. Healing of Cartilage Wounds, *Der Process der Wundheilung mit Einschluss der Transplantation*, *Deutsche Chirurgie*, Stuttgart, Ferdinand Enke, 1901, pt. 16, chap. 18.

22 Matsuoka, M. The Regeneration of Cartilage, *Virchows Arch f path Anat* **175** 1 (Jan.) 1904.

23 Mori, M. Studies on Cartilage Regeneration, *Deutsche Ztschr f Chir* **76** 220, 1905.

24 Malatesta, R. Concerning the Healing of Aseptic Wounds of Hyaline Cartilage from the Perichondrium Covering the Normal Cartilage, *Virchows Arch f path Anat* **184** 123, 1906.

cartilage wound produce young connective tissue, which later may be changed into hyaline cartilage. This change of connective tissue always took place under the influence of the perichondrium.

Haas,²⁵ using the costal cartilage of rabbits for experiments, found that the regeneration of cartilage took place almost entirely from the perichondrium. It proceeded by direct proliferation of all the layers of the perichondrium beneath the outer fibrous tissue. There was found to be a slight amount of regeneration of cartilage from the original cartilage near the perichondrium, but the remainder of the cut end tended to undergo degenerative changes. He also observed that the proliferation of cartilage increased in amounts proportional to the length of time that had elapsed.

METHOD OF STUDY

Fourteen dogs were used in these experiments. In eleven the knee joint was used, in two the elbow, and in one the wrist. The dogs were first fully anesthetized with ether. The knee joints were opened under aseptic precautions, either by a curved infrapatellar incision with the patella tendon cut transversely, or by a long anterior incision with the quadriceps tendon cut transversely. The elbows were exposed by a posterior incision over the olecranon, the triceps tendon being incised transversely. The wrist was exposed by a transverse dorsal incision. The defects in the cartilage were made either with a 5 mm burr through to the subchondral bone or with a scalpel. In some cases, only the most superficial layers of the cartilage were pared off with the scalpel, in others, the cartilage was removed down to the calcified matrix. The condylar ridges of the femur in most cases were traumatized by pounding with a small metal hammer for one minute. In all cases, the joints were closed with great care and all incised tendons carefully approximated. A light plaster cast was applied to the extremity after the operation and left on for from one to two weeks. The dogs were killed in one, two, four, eight and twelve weeks. After death, the blood vessels in the extremities were washed with saline solution, and then india ink was injected into them.

In the knee joint, defects were made in the following areas: patella, internal and external condyles of the femur, internal and external condyles of the tibia, internal and external condylar ridges of the femur, and the upper and lower intercondylar spaces of the femur. In the elbow, the defects were made with the scalpel in the head of the radius, the olecranon fossa of the ulna, the posterior lower humerus and the external and internal condyles of the humerus. In the wrist, defects were made with the scalpel in the scaphoid bone, the semilunar bone and the lower end of the radius.

Gross and microscopic examinations were made of the defects in the joints after the dogs had been killed. Unfortunately, some of the microscopic sections were not clearly cut through the defects, and cannot be included in the analysis of the observations. Sixty-six of the seventy-four sections were satisfactory.

25 Haas, S. L. *Regeneration of Cartilage and Bone with a Special Study of These Processes as They Occur at the Chondrocostal Junction*, Surg. Gynec. Obst. **19** 604, 1914.

The observations have been grouped and analyzed in four ways

1 According to the type of cartilage defect (a) through the superficial layers, (b) through to the calcified matrix, (c) through to the subchondral bone and (d) due to trauma by direct force

2 According to the time elapsed before the dogs were killed (a) twelve weeks, (b) eight weeks, (c) four weeks, (d) two weeks and (e) one week

3 According to the location of the defect in (a) the patella, (b) the condyles of the femur, (c) the condylar ridges of the femur, (d) the intercondylar spaces of the femur and (e) the condyles of the tibia

4 According to the presence or absence of the perichondrium

REGENERATION IN CARTILAGE DEFECTS OF VARIOUS TYPES

Cartilage Defect Through the Superficial Layers—Eight joints were used in this study, divided as follows five knees, two elbows and one wrist. A sharp scalpel was used to pare off the superficial layers of cartilage. Three dogs were killed in eight weeks, two in four weeks, one in two weeks and two in one week.

Gross examination revealed no evidence of healing in the one and two week specimens. The greatest amount of healing in the four week specimens was in the external condyle of the tibia. Here there was noted a definite infiltration of the defect with fibrous tissue. The evidence of repair in the eight week specimens was more marked than in the four week ones. All of the defects in the cartilage were clearly ascertained and the presence or absence of attempted repair was noted.

The microscopic sections were satisfactory in twenty-seven of the twenty-nine areas studied. Five of the seven eight week sections showed regeneration. The clearest evidence of the regeneration of hyaline cartilage was noted in the head of the radius in one of the eight week sections, there were many large, deeply stained new cartilage cells, irregularly placed along one border of the cartilage, between which could be seen fibrils and in this fibrillar structure some blood vessels. Another eight week section of the head of the radius showed many young cartilage cells in the superficial layers about one corner of the defect. An eight week section of the lower intercondylar portion of the humerus presented some deeply stained branching cartilage cells, intermingled with loose connective tissue, which were regarded as evidence of regeneration. In eight week sections of the lower end of the radius and the semilunar bone, it was possible to see new, multinucleated, deeply stained cartilage cells. Three of the eight four week sections showed large quadrilateral cartilage cells on the surface of the defects. It was thought that these might represent an attempt at the formation of new cartilage cells. One two week section of the external condyle of the tibia (fig 1), showed the defect filled with fibrin and granulation tissue, in which were some areas of new fibrocartilage. This defect was adjacent to the margin of the hyaline cartilage, and it appeared that the new fibrocartilage had originated from the old fibrocartilage that is normally present in this region. The cell columns of the deep hyaline cartilage layers on the side of the new fibrocartilage had turned their lines of axis toward the defect. This was thought to represent an early process of regeneration. There was a marked proliferation of perichondrium over the defect in one four week section of an internal condylar ridge, and this was also present in less degree in a four week section of the internal condyle of the femur. A defect in a four week section of the internal condyle of the tibia was partially filled with fibrous tissue, which contained some cartilage cells (fig 2). One two week specimen of the external condyle of the femur, showed the defect filled with fibrin and pus cells, which had the appearance of undergoing

an organization into granulation tissue. One four week specimen of the internal condyle of the tibia and one two week specimen of the condylar ridges showed clefts in the cartilage, the former filled with fibrous tissue, and the latter filled with fibrin. Fibrin could be seen filling the defects in two eight week specimens, three two week specimens, and one one week specimen. Almost all of the sections showed a depression and irregularity of the cartilage edge, which took a pale stain and presented evidence of fibrillation and disintegration of the matrix.

Cartilage Defect Through to the Calcified Matrix—There were eleven joints used in this study, divided as follows: seven knees, two elbows and one wrist. A sharp scalpel was used to pare off the cartilage down to the hard calcified matrix.

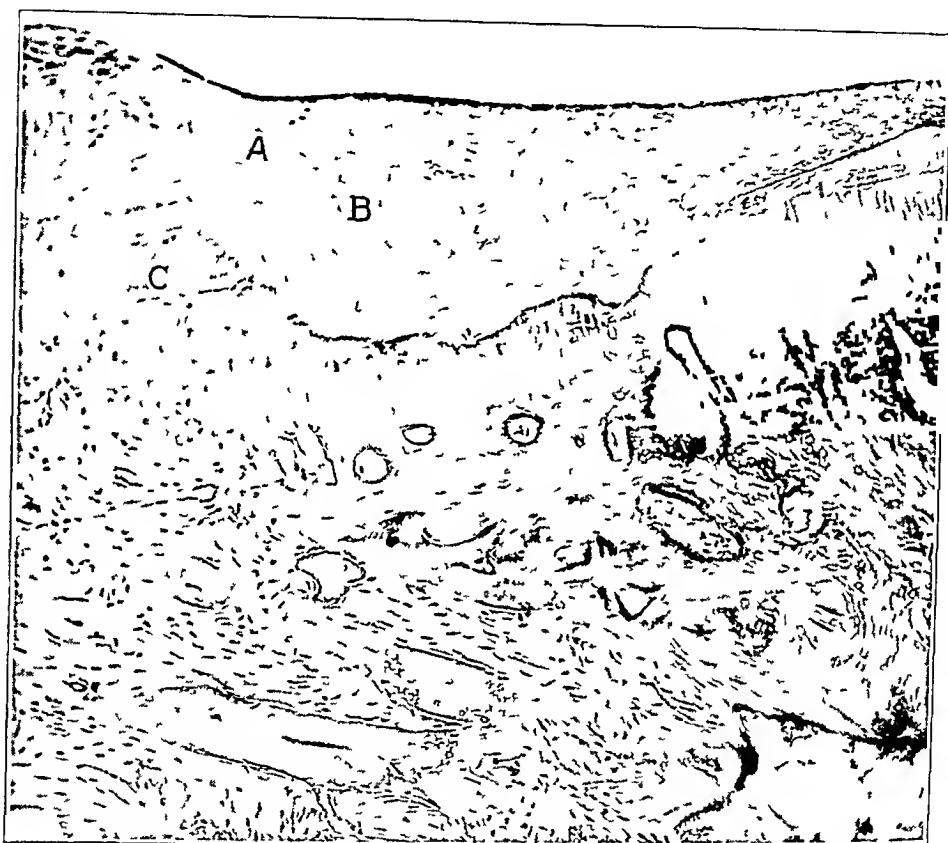


Fig 1—Regeneration of cartilage after two weeks in a defect extending through the superficial layers of the external condyle of the tibia (section 12 f under low power). A, area of new fibrocartilage, B, granulation tissue and connective tissue filling the defect, C, cartilage cell columns of deep layers bending toward the defect.

Two dogs were killed in twelve weeks, three in eight weeks, three in four weeks, one in two weeks and two in one week.

On gross examination, there was no evidence of healing in less than four weeks. The best evidence of healing was observed in the internal condyle of the tibia and the lower intercondylar space of the femur. The patellar surface in both of the twelve week specimens showed a definite smoothing off of the denuded area. The other denuded areas which showed healing were covered with a definite fibrous tissue growth. The scaphoid bone of the wrist in the eight week specimen presented excellent evidence of healing.

The microscopic sections were satisfactory in fifteen of the sixteen areas studied. All of the twelve week sections, one eight week section, and one four week section showed definite evidence of the regeneration of cartilage with the presence of new, deeply stained, large, multinuclear cartilage cells. No regeneration of hyaline cartilage was noted in less than four weeks. The new cartilage cells were found in a proliferation of connective tissue along the denuded margin of the patella in three sections, two of twelve weeks and one of four weeks (figs 3 and 4). There were new cartilage cells adjacent to an increase in hyaline



Fig 2—Regeneration of cartilage after four weeks in a defect through the superficial layers of the internal condyle of the tibia (section 10 e, under high power) *A*, connective tissue pannus on surface of the defect containing spindle cells, *B*, nipple-like process of connective tissue extending into cartilage, containing oval cells and new cartilage cells, *C*, line of calcified matrix.

matrix along one condylar ridge, two patella margins and one scaphoid margin. This new hyaline matrix was lighter stained than the old matrix, and in some places had a fibrillar appearance. It apparently had been produced by the new cells. All of the fibrous pannus covering the denuded cartilage was well vascularized. A great many pale-staining, disintegrating islands of cartilage were observed along the outer edge of the proliferating tissue. There were also some islands of bone along this edge. This bony structure did not take as uniform a stain as the normal bone. Most of the exposed edges of the cartilage showed a

fibrillation of the matrix with an extremely light stain. Some of the denuded areas of the patella and olecranon fossa of the ulna presented areas of fibrocartilage adjacent to which was a proliferation of fibrous tissue containing cartilage cells. Deeply stained fibrin partially filled the defects in two of the one week sections.

Cartilage Defect Through to the Subchondral Bone—Six knee joints were used in this study. The defects were made through the superficial and calcified cartilage layers with a small perforating burr about 5 mm in diameter. Three dogs were killed in twelve weeks, two in four weeks and one in two weeks.

On gross examination, all of the defects in the twelve week specimens could be clearly recognized and showed evidence of healing. The two defects in the external condyle of the tibia showed the largest amount of healing. In none of

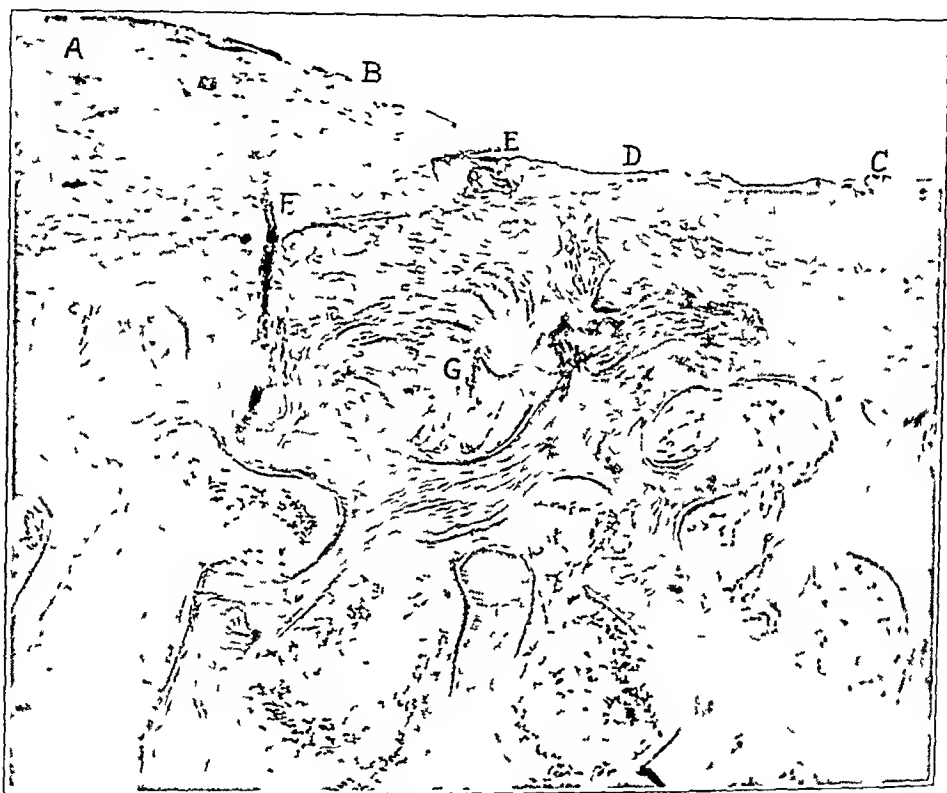


Fig 3—Regeneration of cartilage after four weeks in a defect through to the calcified matrix in the patella (section 7 a, under low power). *A*, pale-staining, disintegrating island of cartilage surrounded by connective tissue, *B*, new cartilage cells on edge of connective tissue pannus, *C*, new cartilage cells surrounded by new hyaline matrix along edge of calcified matrix, *D*, area shown in figure 4 with high power, *E*, bone nodule embedded in connective tissue pannus, *F*, blood vessel growing from subchondral marrow into connective tissue pannus, *G*, subchondral marrow surrounded by normal bone.

these, however, was there the normal glistening appearance of the adjacent non-traumatized cartilage. Fibrous tissue could be seen filling these defects. Granulation tissue filled the defect of one four week specimen. One twelve week experiment showed a defect in the external condyle of the tibia to be well filled with fibrous tissue, while a defect in the internal condyle of the tibia showed fibrous tissue in much smaller amounts.

Twelve of the seventeen microscopic sections studied were satisfactory. As was to be expected from the macroscopic appearances, the twelve week sections presented the greatest amount of regeneration. Three of these sections showed deeply stained, multinucleated cartilage cells (fig 5). Fibrocartilage adjacent to areas of connective tissue containing cartilage cells was observed in contact with these areas of new cartilage cells (fig 6). The defects were all well filled with connective tissue, which became more compact as the edge of the defect was approached. There were many detached islands of cartilage and bone in and on the surface of the defects. These apparently had been broken off by the burr in creating the defects. These islands of cartilage were poorly stained, showed disintegration, and in places were contiguous to fibrous tissue and cartilage cells,

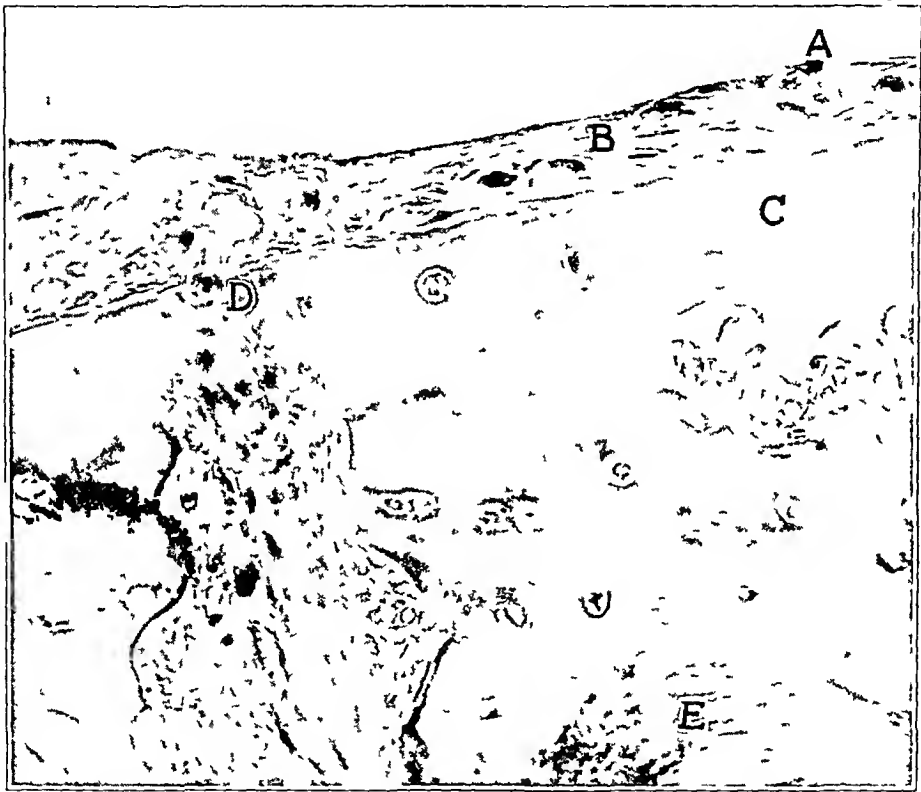


Fig 4—Regeneration of cartilage after four weeks in a defect through to the calcified matrix in the patella (section 7 a, under high power, area D in figure 3). A, young multinucleated cartilage cells, B, connective tissue fibers in new hyaline matrix, C, normal calcified matrix, D, proliferation of connective tissue from the subchondral marrow into fibrous pannus on surface, E, normal bone.

suggesting an early formation of fibrocartilage. The edges of the hyaline matrix adjacent to the defects were bent over and of hooklike appearance. They presented a pale-staining matrix and cells with a border showing disintegration and fibrillation. In one twelve week specimen, the bony edge of the defect showed evidence of bone repair. This margin was sharply demarcated and covered by fibrocartilage. In one four week specimen, all defects contained a moderate amount of fibrin, pus and granulation tissue which was taken to be an evidence of infection.

This joint, grossly, contained a thick sticky exudate. Some of the sections in this joint presented areas of cartilage cells in fibrous tissue adjacent to fibrocartilage. In many sections there was a definite proliferation of connective tissue into the defects from the bone-marrow. One four week section of the upper intercondylar space showed a fibrous layer covering the defect continuous with a fibrous covering of the cartilage on both sides, which was believed to be a perichondrium. Many of the sections presented an extension of the fibrous tissue from the defect over the edge of the adjacent cartilage. There was evidence of fragmentation of the underlying bone in most of the defects, which did not take a normal stain.

Cartilage Traumatized by Direct Force—Six joints were used in this study. After the knee had been exposed, the joint was fully flexed with the patella

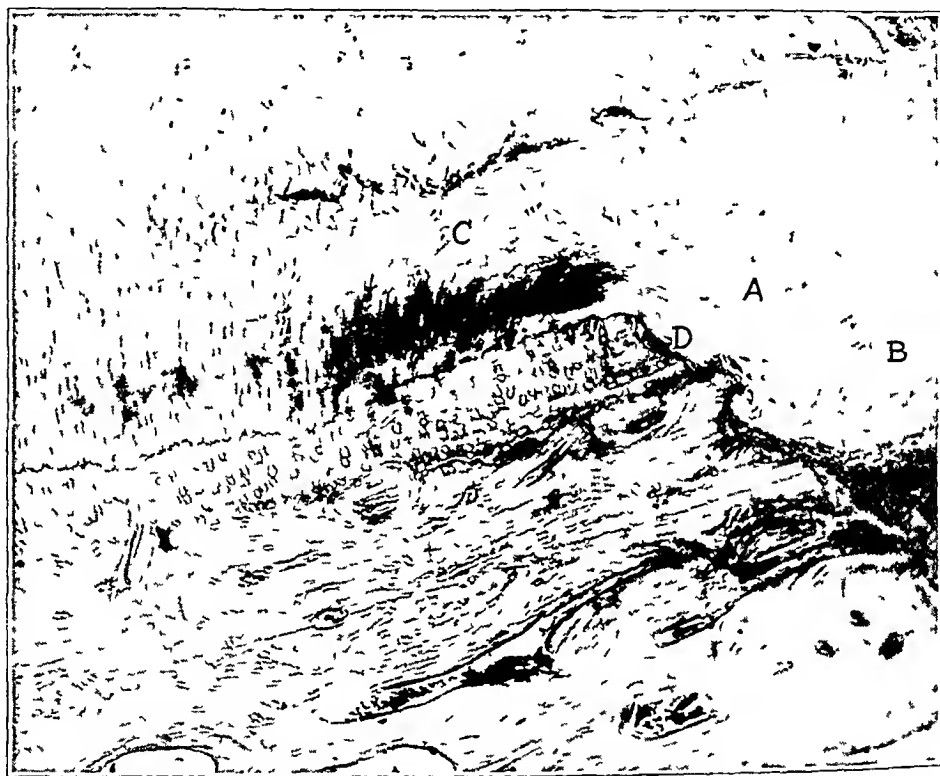


Fig 5—Regeneration of cartilage after twelve weeks in a defect through to the subchondral bone in the internal condyle of the tibia (section 2 d, under low power). A, area of new hyaline cartilage showing large, multinucleated cells and light matrix, B, new fibrocartilage, C, cartilage cell columns of deep layers bending toward the defect, D, healed margin of calcified matrix and bone lining the defect.

dislocated to one side. The cartilage over the lower condylar ridges of the femur was then traumatized by vigorous pounding with a small metal hammer for one minute. One dog was killed in twelve weeks, three in four weeks and one in one week.

On gross examination, the cartilage over the condylar ridges of the twelve week specimen appeared to be flattened. In all of the four week specimens, the cartilage showed little or no gross evidence of trauma. The one week specimen showed evidence of trauma.

The microscopic sections from eleven specimens were satisfactory. Definite evidence of the regeneration of hyaline cartilage was present in two specimens, one of twelve weeks and one of four weeks. Nests of new cartilage cells could be demonstrated taking a deep stain on the internal ridge of a twelve week section. One border of the hyaline matrix was covered by a fibrous layer, which was thought to be perichondrium. The outer layer of hyaline cartilage showed many long spindle-shaped cartilage cells in an irregular arrangement beneath the perichondrium. These were thought to represent new cartilage cells, differentiating

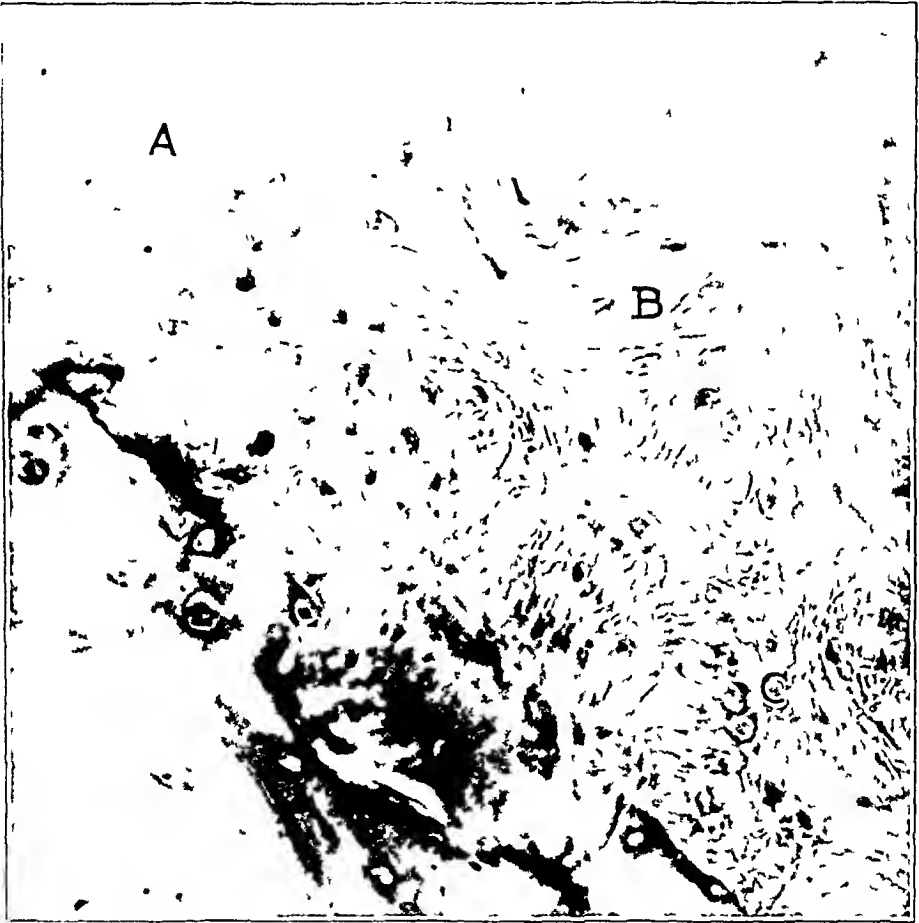


Fig 6—Regeneration of cartilage after twelve weeks in a defect through to the subchondral bone in the lower intercondylar space of the femur (section 3 d, under high power) *A*, large new, multinucleated cartilage cells in new, light-staining matrix, *B*, new fibrocartilage adjacent to new hyaline cartilage, *C*, cartilage cells in connective tissue (connective tissue cartilage) adjacent to new fibrocartilage

from the perichondrium, as was shown by Haas in his costal cartilage experiments. On the internal ridge of the four week section could be seen many well stained, large new cartilage cells. In all of the sections there was observed an irregularity of the cartilage margin along the traumatized ridges with fibrillation and extremely light stained matrix. In four of the condylar ridges there were breaks in the cartilage matrix with long clefts extending obliquely down to the

calcified matrix. In two sections, the line of the calcified matrix was depressed and broken (fig 7), and this was felt to have been caused by the trauma. Some of these clefts contained fibrin and small bits of pale-staining, disintegrating hyaline matrix, as also did some of the indentations on the surface of the ridges. The perichondrium, when present, was lifted up, and in one section red blood cells showed between this and the matrix. In two sections, there was a marked localized thickening of connective tissue, containing fibrocartilage in the form of a protrusion from the hyaline matrix. This was thought to be a reaction to the trauma. In one section, there was disintegration of the traumatized area into cartilage cells and fibrils with the formation of fibrocartilage. This was taken to be a reversion of type from hyaline cartilage to fibrocartilage. In all cases in which a perichondrium was present, this ended at the traumatized area. In

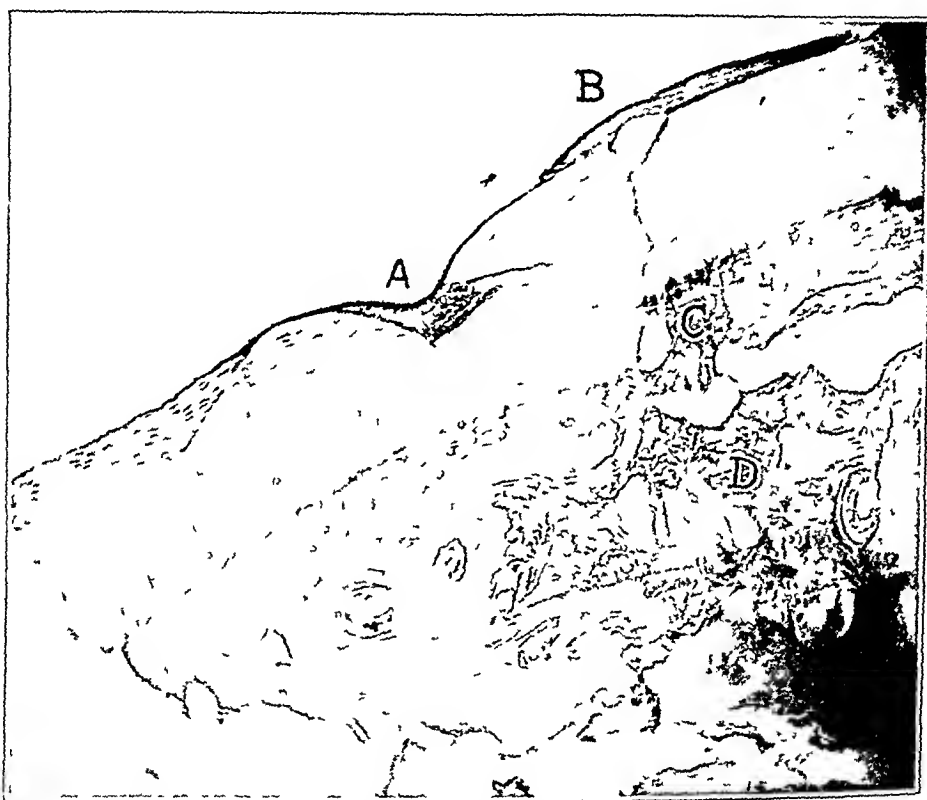


Fig 7—Regeneration of cartilage after one week in external condylar ridge of the femur traumatized by direct force with hammer (section 13 g, under low power). *A*, indentation of the cartilage filled with fibrin, *B*, fibrin on the surface of the cartilage with break in the matrix beneath, *C*, broken and depressed edge of calcified matrix, *D*, fragmentation of bone.

one four week specimen which showed grossly a thick exudate in the joint and was thought to be infected, the traumatized condylar ridges presented a marked depression extending into the subchondral bone. An absorption of the cartilage had occurred, and the defects were filled with well vascularized granulation tissue containing islands of pale-staining, disintegrating cartilage, pus and fibrin. The underlying bone was poorly stained and looked necrotic. Connective tissue from the bone-marrow could be seen penetrating into the spaces. The picture was so different from that seen in the other sections in this group, that the reaction was undoubtedly due to the element of infection added to the trauma.

REGENERATION IN CARTILAGE DEFECTS AFTER
VARIOUS LAPSSES OF TIME

After Twelve Weeks—Eleven defects were produced in three different knee joints. In three of these the defect was made through to the calcified matrix with a scalpel and in seven through to the subchondral bone with a burr, in one the condylar ridges of the femur were traumatized with a hammer.

On gross examination, the best evidence of healing of the defects was in the external condyle of the tibia. The defects here were made into the subchondral bone and were filled with fibrous tissue. The next best evidence of healing was



Fig 8—Regeneration of cartilage after twelve weeks in a defect through the superficial layers in the internal condylar ridge of the femur (section 3 b, under low power). A, area of hyperplasia of new cartilage cells and matrix, showing a protrusion from the cartilage edge.

in the internal condyle of the femur, where the defect had been made into the subchondral bone. There was definite evidence of healing in all of the defects examined.

The microscopic sections from ten of the eleven areas were satisfactory. In seven of the ten there was definite evidence of the formation of new hyaline cartilage. In three of these there were areas of new hyaline cartilage adjacent to new fibrocartilage which, in turn, was adjacent to areas of cartilage cells in connective tissue (fig 6). In two sections, a proliferation of new hyaline matrix could be seen surrounding the new cartilage cells. All of the defects contained

well vascularized connective tissue. One defect made into the subchondral bone in the internal condyle of the femur was apparently lined with a well demarcated and well healed bone margin (fig 5). There were pale-staining and disintegrating cartilage edges and cartilage nodules in the defects.

After Eight Weeks—Ten defects were created in this study in two elbow joints and one wrist joint. In seven, the defect was through the superficial cartilage layers, and in three through to the calcified matrix.

Gross evidence of healing was present in six of the ten defects. The healing did not appear complete, and in some there was evidence of a proliferation of fibrous tissue.

The microscopic sections from all ten areas were satisfactory. In six of the ten, there was evidence of the formation of new hyaline cartilage. The best regeneration was observed in a defect through to the calcified matrix on the radial surface of the scaphoid of the wrist. In this section, along the edge of the incised hyaline matrix could be seen a lighter stained, new hyaline matrix having a fibrillar appearance, in which were contained many nests of new, irregularly placed, deeply stained, multinucleated cartilage cells. The next best area of regeneration was in a superficial defect on the head of the radius, in which new cartilage cells were found surrounded by a matrix having a fibrillar appearance. Young cartilage cells were also found in defects on the posterior surface of the humerus, on the lower end of the radius, on the head of the radius and on the radial surface of the semilunar bone of the wrist. There were cartilage cells in a fibrous pannus in the defects on the olecranon fossa, where the cartilage is normally found to be fibrocartilage. Some fibrin and fibrous tissue were present in some defects.

After Four Weeks—Twenty-five defects were produced in four knee joints. In eight, the defect was through the superficial cartilage layers, in four through to the calcified matrix and in six through to the subchondral bone, in six, the condylar ridges of the femur were traumatized with a hammer.

On gross examination, there was evidence of healing and repair in all of the areas. The best attempt at repair was on the external condyle of the tibia. Fibrous tissue filled some of the defects. In one knee joint, in which a moderately thick exudate suggesting an infection was found, the defects appeared to be filled with granulation tissue.

Twenty-one of the twenty-five sections studied were satisfactory. In two, there was definite evidence of the regeneration of hyaline cartilage. In one of these sections in a defect of the patella through to the calcified matrix (fig 3), there was a marked proliferation of vascularized connective tissue from the perichondrium on one side, and in this tissue were found islands of new hyaline cartilage cells and matrix along with some old, pale-staining, disintegrating islands of hyaline cartilage. Along the incised edge of the cartilage in another portion could be seen some new hyaline matrix containing new cartilage cells. The other section showing regeneration was in the internal condylar ridge which had been traumatized with a hammer. The affected area showed a depression filled with vascularized granulation tissue, pus, fibrin and old, disintegrating, pale-staining cartilage nodules. On one border could be seen some well stained, multinucleated new cartilage cells. This section was from the joint containing the thick exudate referred to. In some of the sections there were large quadrilateral cartilage cells, previously described, which may have represented proliferating cartilage cells. In seven sections there were cartilage cells in connective tissue associated with fibrocartilage partially filling the defect. Many disintegrating old cartilage nodules

were observed in the defects. There were fibrillation and disintegration of the matrix along the edges of the defect. The fibrous pannus, when found filling the defect, showed many injected blood vessels.

After Two Weeks—Thirteen defects were produced in four knee joints. In five, the defect was through the superficial cartilage layers, in two through to the calcified matrix and in four through to the subchondral bone, in two, the condylar ridges of the femur were traumatized with a hammer.

Gross examination revealed no evidence of healing in any of the defects.

The microscopic sections of ten of the thirteen defects were satisfactory. In only one was there any evidence of attempted cartilaginous repair. This was a section of a superficial defect on the external condyle of the tibia (fig. 1). In this section, the defect was partially filled with a loose fibrous pannus showing some blood vessels and fibrin. From one margin there had proliferated a new area of fibrocartilage which was connected with the fibrocartilage adjacent to the hyaline cartilage on the extreme border of the joint surface. The cell columns of the deep layers of hyaline cartilage on one edge of the defect were bending toward the defect. This was shown to be the case in some of Haebler's¹⁰ experiments with regeneration of cartilage. Four of the sections showed fibrin partially filling the defects with an occasional extravasation of leukocytes. Some of this fibrin appeared to be undergoing an organization. The incised edges of the cartilage were generally of a pale stain and showed fibrillation.

After One Week—Fifteen defects were produced in two knee joints. In nine, the defect was through the superficial layers and in four it was through to the calcified matrix, in two, the condylar ridges were traumatized with a hammer.

Gross examination showed no evidence of healing in any of the defects.

The microscopic sections of all fifteen defects were satisfactory. There was no evidence of regeneration of cartilage in any of these sections. In four sections no changes could be noted. In one section of the external condyle of the tibia, there were some deeply stained cartilage cells on the surface which appeared to be of recent origin, but it was not thought that they represented a regenerative reaction. In four sections, the defects were partially filled with fibrin (fig. 7). The traumatized cartilage edge was faintly stained and showed some fibrillation.

REGENERATION IN CARTILAGE DEFECTS IN VARIOUS AREAS OF THE KNEE JOINT

In the Patella—A defect was produced in eight patellae. In two, the defect was through the superficial layers, and in six it was through to the calcified matrix. Two dogs were killed in twelve weeks, three in four weeks, one in two weeks and two in one week.

Gross inspection showed evidence of healing in two of the twelve week specimens, and in one of the four week specimens.

The microscopic sections of all eight specimens were satisfactory. There was evidence of regeneration of cartilage in three. Two twelve week sections showed new cartilage cells in proliferated connective tissue, while one, in addition, showed new hyaline matrix surrounding the new cartilage cells. One four week section showed new cartilage cells in a fibrous pannus, and also new cartilage cells adjacent to new hyaline matrix along the incised cartilage edge (figs. 3 and 4). One four week section showed the defect to be filled with a fibrous pannus containing cartilage cells and fibrocartilage. The fibrous pannus was all well vascularized, and in some sections this was clearly a proliferation of the marginal perichondrium. The incised cartilage edges were faintly stained, and showed evidence of fibrillation.

In the Condyles of the Femur —A defect was produced in eight internal condyles, and six external condyles in eight different knee joints. The defect was through the superficial layers of cartilage in six, through to the calcified matrix in two, and through to the subchondral bone in six. One dog was killed in twelve weeks, three in four weeks, two in two weeks and two in one week.

On gross examination, the most marked healing was noted in the twelve week defect of the internal condyle, which was made through to the subchondral bone. Healing was noted in all of the four week specimens. There was no difference between the healing in the external, and that in the internal condyles.

The microscopic sections of ten of the fourteen areas were satisfactory. The four unsatisfactory sections were on the outer margins of the condyles where the cartilage is normally fibrocartilage. There was no evidence of the regeneration of cartilage in any of the ten sections. Two four week sections through the superficial layers showed large quadrilateral cells on the surface of the cartilage. There were cartilage cells in well vascularized connective tissue in one twelve week section and one four week section of a defect through to the subchondral bone. Fibrin was found partially filling some of the defects. No difference could be ascertained in the power of regeneration in the two condyles.

In the Condylar Ridges of the Femur —A defect was produced in the condylar ridges of ten knee joints. The superficial layers of cartilage were removed in three, the cartilage was incised through to the calcified matrix in one, and it was traumatized with a metal hammer for one minute in six. Two dogs were killed in twelve weeks, four in four weeks, two in two weeks and two in one week.

On gross examination, the twelve week and the four week specimens, in which the cartilage was removed with a scalpel, showed healing. Little evidence of injury could be demonstrated in the condylar ridges which had been traumatized with a hammer, however, some of these showed a flattening of the cartilage.

Sixteen microscopic sections were examined, six of which showed only the internal ridge, six only the external ridge, and four both ridges. New cartilage cells were observed in three of the sixteen sections. Three internal ridges and one external ridge showed this regeneration. One twelve week section with the defect through to the calcified matrix showed new cartilage cells adjacent to an increase in hyaline matrix with a vascularized fibrous pannus filling the defect. There were many nests of new cartilage cells seen in a twelve week section traumatized with a hammer.

In this same section were also seen spindle-shaped cartilage cells, irregularly arranged along the border, and this was thought to represent an early stage of repair. In one four week section of cartilage traumatized with a hammer, new cartilage cells were seen on one side of the defect, which was filled with a vascularized fibrous pannus, fibrin and pus cells. No striking difference was noted between the regenerative changes in condylar ridges traumatized with a hammer and those in cartilage incised with a scalpel. The changes found in the external ridges apparently were the same as those found in the internal ridges.

In the Intercondylar Spaces of the Femur —A defect was produced in four upper intercondylar spaces and in six lower intercondylar spaces in eight knee joints. The defect was through the superficial layers of cartilage in one, through to the calcified matrix in three, and through to the subchondral bone in six. Two dogs were killed in twelve weeks, three in four weeks, one in two weeks and two in one week.

Gross evidence of healing was found in all of the twelve week and four week specimens. In two four week specimens, granulation tissue filled the defect.

The microscopic sections from all ten specimens were satisfactory. In only one twelve week section of a defect in the lower intercondylar space through to the subchondral bone was there any evidence of new cartilage cells (fig 6). This was adjacent to a vascularized fibrous pannus containing cartilage cells and some new fibrocartilage. There were pale-staining, degenerating nodules of hyaline cartilage in this defect. Six of the other nine sections showed cartilage cells either in a fibrous pannus alone or associated with fibrocartilage. A great many of the disintegrating islands of hyaline cartilage were also seen. No difference was noted between the regenerative changes of the upper and those of the lower intercondylar spaces.

In the Condyles of the Tibia—A defect was produced in seven internal condyles and eight external condyles in eight knee joints. The defect was through the superficial cartilage layers in nine through to the calcified matrix in one, and through into the subchondral bone in five. Two dogs were killed in twelve weeks, two in four weeks, two in two weeks and two in one week.

On gross examination the greatest amount of healing was seen in the external condyles. This healing was more marked than that in any of the other areas of the knee joint. There was no healing observed in less than four weeks. In some defects there was a fibrous pannus.

The microscopic sections of eleven of the fifteen specimens were satisfactory. There was evidence of the regeneration of cartilage in two twelve week sections with the defect through to the subchondral bone (fig 5). These showed new cartilage cells with a large amount of fibrocartilage adjacent. A well vascularized fibrous pannus filled one defect which was lined by a margin of healed bone. In one superficial defect of a two week section of the external condyle there was evidence of early regeneration (fig 1). Some sections showed cartilage cells in fibrous tissue partially filling the defect. The margins of the hyaline matrix were faintly stained and presented evidence of fibrillation.

In the Perichondrium—In the earlier periods there was always an element of doubt as to whether articular cartilage was completely covered by an extension of the synovial membrane called perichondrium. Hunter² spoke of demonstrating the perichondrium only with great difficulty and finding that it was adherent. Henle²⁶ said that the epithelium was continued in a thinner layer on the articular surfaces of the cartilage on which it was separated from the cartilage corpuscles by a thin layer of cellular tissue. Toynbee²⁷ wrote that the free surface of articular cartilage was covered by synovial membrane, to which it was attached by a cellular areolar-like tissue. The membrane from the central part of the cartilage showed scarcely any appearance of areolar tissue, being translucent and nearly homogeneous in structure. Soem-

26 Henle, F. G. J. *Müller's Arch.*, 1838, p. 116.

27 Toynbee, Joseph. *Researches Tending to Prove the Non-Vascularity and the Peculiar Uniform Mode of Organization and Nutrition of Certain Animal Tissue, etc.*, *Philosophical Transactions of the Royal Society, London*, 1841, pt. 1, pp. 159-192, *On the Structure of Synovial Membrane Covering the Surface of Adult Articular Cartilage*, *London J. M.* 1 217, 1849.

meining²⁸ and Bichat²⁹ also felt that the synovial membrane covered the surface of the articular cartilage Brodie³⁰ agreed with Bichat and stated that where the synovial membrane was reflected over the articular cartilage it was thin and readily torn, but its existence might always be distinctly demonstrated by careful dissection

Leidy³ Todd and Bowman³¹ and Ogston⁹ of the earlier writers were of the opinion that the synovial membrane covered only the margin of the articular cartilage for a short distance Leidy wrote that it was present in the fetal state over the whole of the articular cartilage, but that after birth it was progressively destroyed from the center to the circumference by pressure and attrition Magendie,³² Velpeau³³ and Cruveilhier³⁴ were of the same opinion Fisher³⁵ wrote that the central area of the articular cartilage had no perichondrium The superficial stratum consisted of flattened cells arranged in groups parallel to the surface The immediate surface was formed of the matrix This superficial layer showed no signs of degeneracy or diminished vitality He further stated that the lateral area of articular cartilage was covered by a delicate extension of the synovial membrane, which toward the center was a close set layer of endothelial cells, which subsequently produced hyaline matrix Davis,³⁶ Strangeways,³⁷ and Ito¹⁹ stated that there was no membrane on articular cartilage In the textbooks on anatomy of Gray³⁸ and of Schaefer,³⁹ it is written that the articular

28 Soemmering, S T *De Corporis Humani Fabrica, Traj ad Moenum, sumpt Varrentrappii et Wenniri, 1794-1801*

29 Bichat, M F X *Organization du systeme cartilagineux, anatomie generale appliquee a la physiologie et la medicine, Paris, 1802*

30 Brodie, Sir Benjamin C *Pathological and Surgical Observations on the Diseases of the Joints, ed 3, London, 1836, p 7*

31 Todd, R B, and Bowman, William *The Physiological Anatomy and Physiology of Man, London, 1856, vol 1, p 88*

32 Magendie, Francois *A Summary of Physiology, translated from the French, Baltimore, E J Coale & Company, 1822*

33 Velpeau, A L M *A Treatise on Surgical Anatomy or the Anatomy of Regions Considered in Its Relation with Surgery, translated from the French by J W Stirling, New York, S Wood & Sons, 1830*

34 Cruveilhier, Jean *The Anatomy of the Human Body, American ed 1, translated from the last Paris edition, New York, Harper & Brothers, 1844*

35 Fisher, A G T *A Study of Loose Bodies Composed of Cartilage or of Cartilage and Bone Occurring in Joints, with Special Reference to Their Pathology and Etiology, Brit J Surg 8 493, 1920-1921*

36 Davis, J S *The Transplantation of Rib Cartilage into Pedunculated Skin Flaps, An Experimental Study, Bull Johns Hopkins Hosp 24 164, 1913*

37 Strangeways, T S P *Observation on the Nutrition of Articular Cartilage, Brit M J 1 661 (May 15) 1920*

38 Gray Henry *Anatomy of the Human Body, ed 20, edited by Warren H Lewis, Philadelphia, Lea & Febiger, 1918*

39 Schaefer, E A *Essentials of Histology, London, Longmans, Green & Company 1916*

cartilage is covered by synovial membrane, except where the opposed articular ends of bones are exposed to friction

With the study of the sections for regenerative changes in cartilage, a careful search was made for evidence of a fibrocellular layer similar to the synovial membrane covering the articular cartilage, which might be called a perichondrium. When this was found to be present, an attempt was made to determine whether this perichondrium played any part in the formation of the reparative tissue. Of the seventy-four sections fifty-nine were satisfactory for determining the presence or absence of a perichondrium. Four of the fifty-nine showed evidence of a perichondrium across all or most of the cartilage border.

1 Over one external condyle of the tibia, which was adjacent to the posterior margin of the cartilage, there was a definite thin fibrous membrane covering the whole edge of the cartilage matrix, which, however, became thinner towards the center. Elongated branching cells were present on the cartilage side of this layer. These cells were separate and distinct from the superficial cartilage cells. In one place, this membrane was stripped back from the underlying cartilage, and showed clearly the fibrillar and cellular structure.

2 There was a thin fibrous membrane over both condylar ridges in a twelve week section of cartilage traumatized with a hammer. In the intercondylar space there was a ligamentous attachment, which was thought to be the attachment of a crucial ligament. The fibrous layer over the cartilage in this section might have been a reaction to the trauma or an extension from the adjoining ligament, and might not have represented a true perichondrium continuous with the synovial membrane. Seggel¹¹ said that when the defect lay close to the insertion of a crucial ligament there was a secondary connective tissue pannus proliferated over the cartilage, which might explain the fibrous layer over the cartilage in this section.

3 In a four week section of the external condylar ridge traumatized with a hammer, a fibrous layer could be seen covering the cartilage on both sides of the ridge, but not over the maximum point. The possibility here is that the fibrous layer represented a true perichondrium but had not been exposed to pressure and friction.

4 In a four week section of the upper intercondylar region, in which the defect was made through to the subchondral bone, there could be seen a dark staining fibrous layer, containing long spindle cells, extending over all of the cartilage margin and defect, which apparently was in no way connected with the underlying cartilage or the connective tissue filling the defect. The cartilage in this section was in the uppermost portion of the intercondylar space close to the margin of the joint, and again had probably not been exposed to friction and pressure.

In twenty-six, or 47 per cent, of the remaining fifty-five sections a perichondrium could be demonstrated over the outer margin of the cartilage. When the defect was close to this margin, there was a proliferation of fibrous tissue of the perichondrium into the defect. Thus, the perichondrium was here taking a definite part in the regeneration. Many of the injured joint areas were not adjacent to the cartilage edges, so that an evidence of a marginal perichondrium would not be looked for. The superficial margin of the cartilage took an extremely dark stain in sixteen, or 29 per cent, of the fifty-five sections. In

places, the most superficial, nonnucleated layer of the cartilage was stripped up, and it could easily be seen how this might be mistaken for a perichondrium. The fibrous tissue, filling the defect in its outer portion, had proliferated for a short distance over the adjacent edge of the cartilage in seven, or 13 per cent, of the fifty-five sections.

In conclusion of this part on the perichondrium, it can be stated that the articular cartilage studied presented a perichondrium only over the margins of the articular edges and in those areas not exposed to pressure and friction. There was evidence of this perichondrium's taking a definite part in the regenerative changes of the cartilage in the lateral defects but not in the central defects.

COMMENT

Macroscopic evidence of healing is not to be noted in the defects of specimens before four weeks. After four weeks or more, the defects showing any reparative changes look as if they have been filled with fibrous tissue. No one of these is covered by tissue having the normal glistening appearance of cartilage. In some specimens, especially in those in which a sticky exudate is present in the joint, the tissue filling the defects looks like granulation tissue. The best gross evidence of repair is in the external condyle of the tibia. The only explanation of this observation is that either the defects have been made close to the margin of the cartilage, or there has been an increased stimulation to effusion of fibrin followed by organization and the formation of connective tissue, owing to the better circulation in the articular vascular circle or in the capillary convolutions of the subchondral bone adjacent to this region of the knee.

Most of the previously reported experimental work has been concerned with the regeneration of cartilage in defects made through to the subchondral bone. There are few references to the regeneration of the superficial layers of cartilage. The results of my experiments show that when the defects are made only in the superficial layers of cartilage, five of the seven eight week specimens show regeneration, as manifested by the presence of new, large, multinucleated cartilage cells. The head of the radius stands out as the area in the elbow and wrist with the most complete regenerative changes. In three of the eight four week specimens, there are some large, distended-looking, quadrilateral cartilage cells. It is thought that these are playing some part in the reparative changes. The same type of cells was described by Pennisi (1904)⁴⁰. One two week section shows a turning of the lines of axis

⁴⁰ Pennisi, A. Sul processo di guarigione delle ferite delle cartilagini, Policlino (sez. chir.) **11** 489, 1904.

of the cell columns in the deeper layers of the cartilage toward the defect (fig. 1). This is shown beautifully in some of the photomicrographs in Hachler's⁴⁰ work on the regeneration of cartilage. The observations in this study namely that in the superficial defects after eight weeks a moderate degree of regeneration of the hyaline cartilage is present and that after two weeks a great many early microscopic evidences of repair are to be seen, do not agree with those of Seggel⁴¹ Fisher,⁴² Ciaccio⁴³ and Hachler.⁴⁴ Some of the defects contain fibrin and some contain fibrin showing evidence of organization. In one four week section of the internal condyle of the tibia (fig. 2) there is a proliferation of fibrous tissue in the defect. The fibrous tissue has spindle cells in the superficial portion and oval cells in the deep part resembling cartilage cells. It penetrates in two places the pale-staining irregular hyaline cartilage border. This confirms an observation of Redfern.⁴⁵ All of these manifestations of attempted repair are conclusive evidence that there is regeneration of cartilage in superficial defects with no involvement of the underlying bone.

The cartilage defect made through to the calcified matrix show slightly more pronounced regenerative changes than the more superficial defects. All of the twelve week sections, one eight week section and one four week section (fig. 3) show large new multinucleated cartilage cells. Some of the defects are partially filled with connective tissue containing cartilage cells. These cartilage cells are thought to have been extended from the adjacent cut edge of the cartilage. This is the cartilaginous callus described by Fisher⁴² and others.

The cartilage defects made through to the subchondral bone show the most complete evidences of cartilage repair. All of the twelve week sections (figs. 5 and 6) show excellently the transitional stage from cartilage cells in connective tissue (connective tissue cartilage) to fibrocartilage to new areas of hyaline cartilage containing the large multinucleated deep-staining cartilage cells. Most of the four week sections show the connective tissue cartilage and fibrocartilage but do not show new areas of hyaline cartilage. Unfortunately there are no sections between twelve and four weeks involving the subchondral bone. Schmidt (1923)⁴¹ showed the presence of this connective tissue cartilage after eighteen days, and also a beginning proliferation of new cartilage cells. Many of the sections show the subchondral marrow playing a part in the regeneration. This is accomplished by the proliferation of connective tissue into the defect. Such connective tissue takes part in the formation of connective tissue cartilage. This was shown by Tizzoni,⁴⁶ Rimann⁴⁶ and Ito.⁴⁷ Many disintegrating pale-staining cartilage islands are

41 Schmidt A. Experimentelle Untersuchungen über das Schicksal teilweise ausgeloster Knorpelknochenteile von der Gelenkfläche des Kniegelenkes, Beitr. z. klin. Chir. **130** 142 1923-1924.

observed, surrounded by and intimately connected with fibrous tissue. The margins of the cartilage adjacent to the defects all show various degrees of fibrillation and disintegration, and are very lightly stained. In some of these areas of disintegration there are areas of regeneration with new cartilage cells and new matrix. This was observed by Gies.¹³

The cartilage traumatized by pounding with a metal hammer shows definite regenerative changes. Large new cartilage cells are seen on the internal condylar ridge of one twelve week section and one four week section. These new cells are never found in the superficial layers of cartilage, but are in the adjoining layers. In some sections there is an increase of hyaline matrix about these cells. The margin of the cartilage is generally faintly stained and presents a disintegrating border with small cartilage cells. In my experiments, all of these new areas of cartilage formation are well circumscribed. Seggel¹⁴ mentioned this fact. Fisher,³⁵ after traumatizing cartilage for two minutes with a hammer, found no change after five weeks. This is not in accord with my observations. Many of the sections show clefts in the cartilage due to the trauma. These clefts are filled with pale-staining, disintegrating cartilage nodules and fibrin undergoing organization into granulation tissue. In two sections a localized connective tissue thickening is present over the maximum point of the ridge, which contains fibrocartilage. This is undoubtedly a reaction to the trauma. The specimen of a knee filled with a thick sticky exudate, suggesting an infection, shows a similarity to the experimental case of Fisher,³⁵ in which he injected *Streptococcus salivarius* in broth culture into a knee previously traumatized with a hammer. He found that the knee was filled with creamy pus, that the synovial membrane was converted into granulation tissue and that there was some absorption of the articular cartilage. In my specimen there was complete absorption of the articular cartilage over the traumatized area with a proliferation of granulation tissue, pus and fibrin in the absorbed area.

The element of time required to show different types of regenerative changes in the cartilage has produced some interesting observations. The earliest microscopic evidence of repair is the fibrin formation, which is seen as early as one week (fig 7). After two weeks in some of the sections there is definite evidence of the organization of fibrin and of the occurrence of granulation tissue (fig 1). These observations are mentioned by a great many investigators. The granulation tissue is then observed to change into connective tissue, which is found in the four week sections (fig 2). In one third of the four week sections cartilage cells are present in connective tissue and fibrocartilage. There is also seen a disintegration of bits of old, pale-staining cartilage into connective tissue, which then undergoes changes into connective tissue cartilage and fibrocartilage. It is interesting to note from the work of

Maichand²¹ that the changes in perichondrium covered cartilage are essentially the same as those I found in articular cartilage. There are definite evidences of new cartilage cells in 70 per cent of the twelve week sections, 60 per cent of the eight week sections, and 10 per cent of the four week sections. No new cartilage cells are seen in less than four weeks, however, in one two week section (fig 1) there is a bending of the cell columns of the deep layers of the cartilage toward the defect with an area of new fibrocartilage. Many of the four week and eight week sections showing new cartilage cells on the margin of the hyaline matrix (fig 3) show a proliferation of new, finely fibrillar hyaline matrix about these new cells. This new matrix apparently has been formed by the new cartilage cells themselves. This was observed by Haebler²⁰ in superficial defects after 225 days.

The comparative study of regeneration in different areas of the knee joint has not disclosed any one area which has greater regenerative powers than the others. Probably the best pictures of regeneration are to be seen along the denuded margins of the patella (fig 3). A proliferation of fibrous tissue from the adjacent synovial membrane seems to play a large part. In three sections of the patella, new areas of hyaline cartilage are to be seen in connective tissue, which is adjacent to connective tissue cartilage. In another section of the patella, fibrocartilage is observed with connective tissue cartilage, but no new hyaline cartilage is seen. The condylar ridges of the femur have presented nests of new cartilage cells in three sections (fig 8). The internal ridge has been the most frequently affected. These condylar ridges, however do not show the cartilaginous callus. There are not sufficient microscopic sections of the condyles of the tibia to confirm the gross observations, namely, that the best evidence of repair is to be found in the defects in the external condyle of the tibia. Two of the tibial sections show new cartilage cells in twelve weeks, while one two week section shows early changes but no new cartilage cells. In the defects in the condyles of the femur and intercondylar spaces, there are many evidences of cartilaginous callus, but only one section shows new multinucleated cartilage cells.

Haebler²⁰ found that after placing the legs of dogs in plaster following the creation of defects in the cartilage there was a definite disturbance of healing in the defects. In my experiments, all of the joints were placed in plaster immediately after the operation, and the plaster was allowed to remain on from one to two weeks. The casts were then removed and the dog was allowed to move the joint. The fact that the joints were immobilized for this short time and the normal physiology of the joints disturbed may have had an effect on the degree and amount of regeneration in the cartilage defects.

SUMMARY AND CONCLUSIONS

Experiments have been performed on the joints of fourteen dogs in order that a study might be made of the regeneration of the hyaline cartilage in superficial and deep defects, and of the reaction of this cartilage to direct trauma. These dogs were killed in from one to twelve weeks after the injuries to the cartilage. The more important contributions in the literature on this subject have been reviewed and correlated with the observations reported here.

The results of these studies show that hyaline cartilage in joints does not regenerate in less than four weeks. The best evidences of regeneration are found in twelve weeks.

In these regenerative changes the following tissues have been observed to appear: first, fibrin, second, granulation tissue, third, connective tissue, fourth, cartilage cells in connective tissue (connective tissue cartilage), fifth, fibrocartilage, and sixth, new hyaline cartilage.

Regeneration of hyaline cartilage has been found in superficial defects not involving the subchondral bone. The greatest amount of regeneration, however, is seen in those deep defects which do involve the subchondral bone.

Hyaline cartilage is observed to react occasionally to direct trauma with a proliferation of nests of new cartilage cells.

No striking difference in the regenerative powers of cartilage in different areas of the knee joint can be demonstrated.

No definite evidence of a perichondrium covering the articulating surfaces of hyaline cartilage has been observed.

In these experimental studies there was enough evidence of hyperplasia of cartilage as a result of injury and trauma to justify further experimentation.

PROTOCOL OF EXPERIMENTS

EXPERIMENT 1—The knee joint was used, and the defects were made with a burr through to the subchondral bone in the internal condyle of the femur and the external condyle of the tibia. The dog was killed twelve weeks after the operation.

Internal Condyle of the Femur—On gross examination, the defect could be clearly seen and showed evidence of healing. The microscopic section was cut through the center of the defect. This center was filled with a well-vascularized fibrous pannus. At one edge in the fibrous tissue were cartilage cells which appeared to have arisen from the deeper layers of the adjacent cartilage. This fibrous tissue at one edge extended over the cut edge of the cartilage. The cartilage cells and the matrix were faintly stained along the edges and the matrix showed beginning disintegration. There was a hooklike projection of old cartilage into the fibrous pannus at one edge. When the defect was being created with the burr, the cartilage most likely bent in at this point before breaking. Over part of the defect extended a fibrocellular membrane with elongated fusiform cells, which was suggestive of a perichondrium. Outside the fibrous pannus lay several nodules of bone and cartilage, which were pale-staining and showed evidence of disintegration.

External Condyle of the Tibia—On gross examination, almost complete healing was evident, the defect being recognized with difficulty. The microscopic section was not cut through the traumatized area. Over the whole cartilage area extended a thin fibrous membrane with fusiform cells, which became thicker toward the margins. On the cartilage side of this, branching cells were seen. These were distinct and separate from the uppermost cartilage cells. In one place, this membrane had been stripped back and showed beautifully the fibrillar structure and cells. This was believed to be perichondrium.

EXPERIMENT 2—The knee joint was used, and defects were made with a scalpel and a burr in the patella, the condyles of the tibia and the lower intercondylar space of the femur. The condylar ridges of the femur were traumatized with a hammer. The dog was killed twelve weeks after the operation.

Patella—The defect extended through to the calcified matrix. On gross examination, the surface of the patella was beginning to look smooth. The microscopic section was cut through the center of the defect. From the synovial membrane on one margin, there was a proliferation of connective tissue, which extended over a large part of the defect. In the central portions of this, cartilage cells were seen, with early formation of hyaline matrix. The cells were larger and looked more immature toward the growing edge. The connective tissue was well filled with blood vessels. Along the margin of the incised hyaline matrix in another portion of the defect, there were well demarcated areas of new hyaline matrix, which contained well stained, large new cartilage cells. Over one side of the cartilage for a short distance was a thin fibrous membrane with blood vessels, which was believed to be perichondrium.

Condylar Ridges of the Femur—The cartilage was traumatized with a hammer. Gross examination showed the cartilage over the ridges to be somewhat flattened, but otherwise normal. The microscopic section was clearly cut through the traumatized areas. The edges of the matrix over the ridges were faintly stained and showed disintegration and fibrillation. In the internal ridge were many large nests of new cartilage cells with well stained nuclei. These were not found in the superficial layers of cartilage but in the adjoining layers. The cartilage cells along some of the borders of the defect were spindle-shaped and had no regularity of arrangement. A fibrillar membrane containing fusiform cells covered most of the cartilage area, being absent over only one small area of the ridge. This was continuous with the ligament attached in the intercondylar space, which was thought to be a crucial ligament.

Lower Intercondylar Space—The defect extended through to the subchondral bone. Gross examination showed that the defect was well filled with fibrous tissue. The microscopic section was cut through the center of the defect. This was well filled with a vascularized fibrous pannus with some disintegrating bone nodules on the surface. On the edges of the defect was a fibrillation of pale-staining cartilage, which was adjacent to fibrous tissue containing cartilage cells. The fibrous tissue filling the defect extended over the cartilage on one edge. The synovial membrane extended over the cartilage for a short distance on one side. Away from the defect, a break in the cartilage through to the bone-marrow could be seen, and this cleft was partially filled with vascularized connective tissue which had proliferated from the subchondral marrow.

Internal Condyle of the Tibia—The defect extended through to the subchondral bone (fig 5). On gross examination, there was definite evidence of fibrous tissue filling the defect. The microscopic section passed through the center of the defect. The defect was well filled with a vascularized fibrous pannus, and on

both sides could be clearly seen many nests of new, deeply stained cartilage cells adjacent to fibrocartilage, which covered the whole inner margin of the defect. The inner margin of the defect had a well healed calcified margin. In the outer portion of the defect, there was an island of disintegrating cartilage adjacent to fibrocartilage. The old cartilage had the appearance of disintegrating into fibrous tissue and then forming fibrocartilage. There was a fibrillation of the outer margin of the original cartilage with a pale stain. The fibrous tissue from the defect was growing over one edge of the cartilage.

External Condyle of the Tibia—The defect extended through to the subchondral bone. On gross examination, it was seen that fibrous tissue filled the defect. The evidence of repair was much more marked than that seen in the defect on the internal condyle of the tibia. The microscopic section showed only one edge of the defect. The edge of the hyaline matrix was pale-staining and disintegrating, and showed an adjacent area of fibrocartilage between this and the bone. In the hyaline matrix were some irregularly shaped cartilage cells containing many nuclei, which were thought to be new cells. Between these new cells fibrils could be seen. Many blood vessels were present in the neighboring fibrous pannus. In the connective tissue about the fibrocartilage were many cartilage cells. For a short distance from the defect there was a proliferation of fibrous tissue over the cartilage edge.

EXPERIMENT 3—The knee joint was used, and the defects were made with a scalpel and a burr in the patella, the condylar ridges and the upper and lower intercondylar spaces. The dog was killed twelve weeks after the operation.

Patella—The defect extended through to the calcified matrix. Gross examination revealed evidence of healing. The microscopic sections showed a breaking away of cartilage, in places, from the bone along the line of calcification. The defect was not filled with any tissue. From one margin of the cartilage, the synovial membrane, which contained some spindle cells, had extended over the hyaline matrix for a short distance. Along this surface of the cartilage there were some deeply stained, new, multinucleated cartilage cells. On one side, the matrix and the cells were pale-staining, and the edge of the matrix looked frayed.

Condylar Ridges—The defect was made through to the calcified matrix (fig 8). Gross inspection showed evidence of healing, but the external ridge looked irregular. The microscopic section passed through both defects. The defects were filled with a vascularized fibrous tissue pannus, containing no cartilage cells. On the internal ridge, in the outer zone of the cartilage were new, deeply stained, irregularly arranged cartilage cells. The hyaline matrix projected over this area. The same new cells, in fewer numbers, were present on the external ridge. Some of the cartilage cells adjacent to the defects had a pale stain, and the matrix showed fibrillation. In spots on the surface there was a dark-staining, nonnucleated layer of cartilage which was thought to be only an outer layer of cartilage.

Upper Intercondylar Space—The defect extended through to the subchondral bone. Gross inspection revealed evidence of healing. The microscopic section was poor. The defect was filled with well vascularized fibrous tissue and granulation tissue. The edge of the bone around the defect was well demarcated and well healed. Some giant cells were seen around the edges of the bone. Along some of the borders were a few large cells in fibrous tissue, which looked like cartilage cells.

Lower Intercondylar Space—The defect extended through to the subchondral bone (fig 6). Gross examination showed evidence of healing. The microscopic

section passed through the defect, which was filled with fibrous tissue and granulation tissue with many blood vessels. On one margin of the cartilage, the cell columns in the deeper layers bent their lines of axis toward the defect, adjacent to which were many large, deeply stained new cartilage cells. Fibrocartilage was contiguous with these new cells, and connective tissue containing cartilage cells was next to this. On the outer edge of the cartilage, close to the new cells was pale-staining, disintegrating matrix. Along the borders of the defect were two old cartilage islands showing disintegration. The fibrous tissue from the defect had extended over the edge of the cartilage for a short distance.

EXPERIMENT 4—The elbow joint was used, and the defects were made with a scalpel in the head of the radius, the olecranon fossa of the ulna and the posterior surface of the humerus. The dog was killed eight weeks after the operation.

Head of the Radius—The defect extended through to the superficial layers. It showed macroscopic evidence of healing. The microscopic section showed hyaline cartilage on three sides of bone. The defect could be clearly ascertained. About one corner of this were deep-stained cartilage cells with many nuclei intermingled with more lightly stained cartilage cells. The former were thought to represent new cartilage cells. The edges of the cartilage showed disintegration and fibrillation with an irregular border and some debris attached. The superficial layer in spots showed deep staining and was nonnucleated. Over the hyaline cartilage for a short distance, on one side, there was an extension of the fibrous covering of the normal fibrocartilage. This was the only evidence of a perichondrium.

Olecranon Fossa of the Ulna—The defect extended through to the calcified matrix. Macroscopically, it showed definite evidence of healing. The microscopic section showed the olecranon fossa to be covered on both margins with hyaline cartilage, but the main portion of the indentation was covered with fibrous tissue containing some cartilage cells. The bone was extremely compact and contained little or no marrow cavity. Along the margin of the bone were many giant cells. On the margin of the cartilage were the capsules of cartilage cells which have been emptied of their nuclei. Covering part of the hyaline cartilage was a small area of fibrous tissue with fusiform cells going into a deep-staining, nonnucleated superficial layer of cartilage. This was the only evidence of a perichondrium. In the hyaline matrix adjacent to the fibrous covering were several deeply stained, branching cartilage cells, which it was thought might be embryonic cartilage cells.

Posterior Lower End of Humerus—The defect extended through the superficial layers. Gross examination revealed evidences of healing. The microscopic section showed the defect clearly. In the defect, loose connective tissue was found with some deep-staining, branching cells, which were taken to be embryonic cartilage cells. Between the connective tissue and the normal hyaline matrix was a lighter staining area of hyaline matrix. This may have been new matrix. On one margin could be traced for a short distance a fibrous layer which extended from the synovial membrane. This was the only evidence of a perichondrium. There was a deep-staining, nonnucleated border of cartilage to most of the matrix.

EXPERIMENT 5—The elbow joint was used, and the defects were made with the scalpel in the head of the radius, the olecranon fossa of the ulna, and the external and internal condyles of the humerus. The dog was killed eight weeks after the operation.

Head of the Radius—The defect extended through the superficial layers. No macroscopic examination was made. The microscopic section showed the denuded area. Over this defect extended a fibrous layer from the cartilage edge. The superficial portion of the cartilage showed an increased number of cartilage cells.

which were deeply stained and irregularly placed, and between which in places were fibrils. The adjacent hyaline matrix was faintly stained. A few blood vessels were found in this new cartilage structure.

Olecranon Fossa of the Ulna—The defect extended through to the calcified matrix. Macroscopic examination was not made. The microscopic section showed the indentation of the fossa, which was filled with fibrous and granulation tissue. In the fibrous tissue, adjacent to the bone, were some cartilage cells. Hyaline cartilage was not present. It is the impression after studying this section and the other one of the olecranon fossa that the bone here was normally covered with fibrocartilage.

External Condyle of the Humerus—The defect extended through the superficial layers. Gross examination was not made. The microscopic section showed the depression in the cartilage. In this defect no fibrin or connective tissue was present. There was an extension of a fibrous membrane from the synovia for a short distance over the cartilage. This was the only evidence of a perichondrium. Some lighter staining, wavy areas ran longitudinally through the hyaline matrix beneath the incised area, these were thought to be artefacts.

Internal Condyle of the Humerus—The defect extended through the superficial layers. Gross examination was not made. The microscopic section showed the defect clearly. The margin of this was irregular and covered with fibrin and debris. In the cartilage beneath, some elongated cartilage cells were present, but no new cartilage cells. In places, the margin of the cartilage was deeply stained and had been detached. The only evidence of a perichondrium was shown on one edge, where the fibrous tissue had extended for a short distance over the cartilage.

EXPERIMENT 6—The wrist joint was used, and the defects were made with a scalpel in the scaphoid bone, the semilunar bone and the lower end of the radius. The dog was killed eight weeks after the operation.

Scaphoid Bone—The defect extended through to the calcified matrix. There was macroscopic evidence of healing. The microscopic section was clearly cut through the defect. A layer of light-staining, hyaline matrix containing fibrils was superimposed on the normal-staining matrix over the extent of the incised area. Contained within this layer of lighter matrix, in places, were large, new, deeply stained, multinucleated cartilage cells. Some of the nuclei in these showed beautiful mitosis and division. Some of the new cartilage cells could be seen proliferating from the superficial cartilage cells. The edge of the matrix was fairly regular. Over the marginal edges of the hyaline matrix was a fibrous membrane, which was the only evidence of a perichondrium.

Semilunar Bone—The defect extended through the superficial layers. There was macroscopic evidence of healing. The microscopic section showed an irregular border to the incised area. Along the margin of the matrix in the defect were many large, deeply stained, multinucleated cartilage cells. These were irregularly placed and were believed to represent a regeneration of cartilage. Along the margin of the cartilage were many elongated cartilage cells. Hyaline cartilage was on two sides of the bone, with fibrous and connective tissue on a third side. There was no evidence of a perichondrium.

Lower End of the Radius—The defect extended through the superficial layers. There was gross evidence of healing. The microscopic section showed a deposit of fibrin and debris on the surface of the defect. In this fibrin were some large round cells which were similar to types of cartilage cells. Along the surface

were many multinucleated, irregularly placed cartilage cells which did not take a deep stain. These were new cartilage cells. There was a transverse break in the whole of the cartilage matrix in the middle of the incised area. There is a deep-staining, nonnucleated, superficial layer of cartilage, which in places had been stripped back and was broken. At both marginal edges, the fibrous tissue extended for a short distance over the cartilage and was continuous with this darkly stained superficial layer. This was the only evidence of a perichondrium.

EXPERIMENT 7—The knee joint was used, and the defects were made with the knife in the patella and with the burr in the upper intercondylar space and the internal condyle of the femur. The condylar ridges of the femur were traumatized with the metal hammer. The dog was killed four weeks after the operation.

Patella—The defect extended through to the calcified matrix (figs 3 and 4). Macroscopic examination was not made. The microscopic section showed the incised area clearly. Over about one half of the defect there was a proliferation of connective tissue, which had come from the synovial membrane covering the outer margin of one edge of the hyaline cartilage. This connective tissue pannus was thickest toward the center of the defect and gradually became thinner as the edge of the defect was approached. It contained small islands of new hyaline matrix with new, deeply stained, multinucleated cartilage cells. Adjacent to these were cartilage cells in connective tissue (connective tissue cartilage). Also contained in this fibrous pannus were small islands of old cartilage undergoing fibrillation and disintegration, with faint cell nuclei. The connective tissue was closely adherent to these islands of old cartilage. Small bits of broken off calcified matrix were observed in the connective tissue pannus. Along the incised border of the hyaline matrix not covered with the connective tissue, there were large, new, multinucleated cartilage cells surrounded by new, pale-staining matrix. These cells appeared to have arisen from the cartilage cells in the superficial layers. The mitoses of the cell nuclei could be seen. Blood vessels were present in the connective tissue pannus.

Upper Intercondylar Space of the Femur—The defect extended through to the subchondral bone. Gross examination was not made. The microscopic section passed through the center of the defect. The defect was filled with a connective tissue pannus, which was well vascularized. The pannus was thicker and denser toward the surface of the defect. In the lower portion toward the bone there were rather large, circumscribed spaces filled with blood. In the pannus were a few pale-staining, disintegrating islands of old cartilage to which the connective tissue was closely adherent. The outer margins of these had a fibrillar appearance. The edges of the hyaline matrix on the sides of the defect projected. The cartilage was faint-staining and showed fibrillation and was closely adherent to the connective tissue in these places. The connective tissue in these portions of the defect contained many cartilage cells (connective tissue cartilage). On one side of the defect, the cartilage was bent down over the cut edge of the calcified matrix in a hooklike projection. There was a dark-staining fibrous layer containing long fusiform cells which extended over the fibrous pannus of the defect and the cartilage on both sides. The continuity of this was not broken, and it was in no way connected with the underlying cartilage in structure. This was believed to be definitely a perichondrium.

Internal Condyle of the Femur—The defect extended through to the subchondral bone. Gross examination was not made. The microscopic section showed only one portion of the defect. This portion was filled with loose connective

tissue which contained many blood vessels. The connective tissue was denser on the surface than toward the bony margin. It was closely adherent to the hyaline matrix on one side, but did not extend over the cartilage. The edge of the hyaline matrix was faint-staining compared with the normal hyaline cartilage farther away. There were many islands of pale-staining, disintegrating cartilage in the connective tissue pannus filling the defect. In the connective tissue adjacent to the bone were many cartilage cells and some areas of early fibrocartilage. The superficial layer of cartilage, which was nonnucleated, was stripped up for a short distance but was not deeply stained as had been so often observed. There was no evidence of any fibrocellular layer which might be called a perichondrium.

Internal Condylar Ridge—The cartilage was traumatized with a metal hammer. Gross examination was not made. The microscopic section showed the traumatized area. Most of the cartilage was covered by a rather thick fibrocellular layer which took a dark stain. The cells were long and fusiform. In one place, this fibrous layer, which was thought to be a definite perichondrium, was lifted up from the matrix and there it had a few red blood cells beneath it. The matrix here was of irregular contour and took an uneven stain. The border of cartilage not covered by the perichondrium showed fibrillation and disintegration. There was one long irregular break in the cartilage matrix, extending from the surface of the cartilage obliquely backward to the calcified matrix, the line of which it followed for a short distance. In the widest part of this cleft were many irregular sequestrations of cartilage with faint-staining matrix and cells, showing fibrillation about their borders.

External Condylar Ridge—The cartilage was traumatized with a metal hammer. Gross examination was not made. The microscopic section showed clearly the traumatized portion of the ridge. A fibrous layer extended over the cartilage in the intercondylar space, ended at the beginning of the prominence of the ridge, and was continued again on the other side. This was believed to be a perichondrium. The cells in this were long and fusiform. The cartilage over the prominence of the ridge was somewhat disintegrated on the surface. Parallel to the surface, in the middle layers of the cartilage, was a cleft, which was thought to be due to the trauma. About this cleft, the cartilage took a distinctly lighter stain. There was no large amount of fragmentation of cartilage, and no new cartilage cells were seen.

EXPERIMENT 8—The knee joint was used, and the defects were made with the scalpel and the burr in the patella, the external and internal condyles of the femur and the upper and lower intercondylar spaces. The condylar ridges of the femur were traumatized with a metal hammer. The dog was killed four weeks after the operation.

Patella—The defect extended through to the calcified matrix. On gross examination, a thick sticky exudate was found covering the patellar surface of the joint. The microscopic section was not cut clearly through the denuded area. The incised area, however, was partially covered with fibrous tissue, which contained some cartilage cells. On one side of the defect a well formed area of fibrocartilage could be seen, with deeply stained cells and fibrils. In the fibrous pannus were some areas of hyaline matrix, which showed disintegration. Many blood vessels coursed through the fibrous pannus.

External Condyle of the Femur (Outer Side)—The defect extended through to the subchondral bone. Gross inspection showed it to be filled with granulation tissue. The microscopic section confirmed this observation and showed the presence

of fibrous tissue. A few areas of fibrocartilage were attached to the bone. The cartilage on this joint area was normally fibrocartilage. Hyaline cartilage was not seen. The fibrous pannus was well vascularized.

Internal Condyle of the Femur (Outer Side)—The defect extended through to the subchondral bone. On gross examination, the defect was found to be filled with granulation tissue. The microscopic section showed no hyaline cartilage. The defect was filled with granulation and fibrous tissue, containing many blood vessels. Fibrocartilage was seen along the edges of the calcified matrix and along the bone margin of the defect.

Upper Intercondylar Space—The defect extended through to the subchondral bone. On gross examination, a thick, sticky joint fluid with granulation tissue filled the defect. The microscopic section passed clearly through the defect. The defect was filled with granulation tissue containing many blood vessels. On the surface of the defect, much fibrin and many pus cells were found, with one large organized mass. Pus and fibrin were also contained in the granulation tissue. The edges of the cartilage on both sides were well demarcated, but were pale-staining with fibrillation and disintegration. Some of the connective tissue adjacent to this cartilage contained cartilage cells. There were no new hyaline cartilage cells present. In the granulation tissue was an old, pale-staining, disintegrating nodule of cartilage which was being penetrated by the surrounding tissue. The connective tissue on one side of the defect extended for a short distance over the cartilage edge. The margin of the hyaline matrix showed some fibrillation and pale staining.

Lower Intercondylar Space—The defect extended through to the subchondral bone. Gross examination showed a thick, sticky joint fluid, with the defect filled by granulation tissue. The microscopic sections showed the defect on one side of the cartilage. The defect was filled with granulation tissue containing many blood vessels. Pus and fibrin were found on the surface of the defect and extended over the edge of the hyaline cartilage. As the edge of the bone and cartilage was approached, the granulation tissue changed into fibrous tissue. This fibrous tissue contained some cartilage cells, and also some areas of typical fibrocartilage. The surface of the defect showed rather compact fibrous tissue with blood vessels, which was similar to a perichondrium. This, however, did not extend over the hyaline cartilage. It was thought that the section was probably cut in that portion of the intercondylar space which was adjacent to the border of the hyaline cartilage.

Internal Condylar Ridge—The cartilage was traumatized with a hammer. On gross examination, a thick, sticky exudate was found in the joint, with a depression over the ridge. The microscopic section was clearly through the traumatized area. This area showed a depression into the bone with an absorption of cartilage, and resembled the areas made with a burr through to the subchondral bone. The defect in the cartilage was filled with granulation tissue containing a large amount of fibrin and pus. The surface of the granulation tissue, as well as the remaining cartilage, was covered with a thin layer of pus and fibrin. A fibrous layer covered the defect and continued for some distance over the cartilage on one side. The lower portion of this layer contained some cells that looked like elongated cartilage cells. On one margin of the defect, the hyaline matrix projected into the granulation tissue, this projection took a pale stain and showed disintegration and fibrillation. On the other margin of the defect was the same type of cartilage, which showed evidence of connective tissue having penetrated its outer border. On the surface of this hyaline matrix were large, well stained cells, which resem-

bled new cartilage cells. In the matrix were small spaces that resembled lacunae. There was a penetration of the granulation tissue filling the defect with connective tissue proliferating from the bone-marrow. The tissue in the defect was well vascularized. The surrounding bone did not take the normal stain and looked somewhat necrotic. The remarkable fact about the section was that the trauma from the hammer had caused so much destruction in the cartilage and underlying bone. With so much pus and fibrin there must have been infection. The picture was probably the result of the reaction to trauma and infection. Unfortunately, the joint fluid was not cultured.

External Condylar Ridge—The cartilage was traumatized with a hammer. Gross examination showed a thick, sticky exudate in the joint, with a depression over the ridge. The microscopic section was cut through the traumatized area. As was the case in the internal ridge, there was a depression in the bone with an absorption of the cartilage over the ridge. This defect was filled with granulation tissue which contained a great many blood vessels. The cartilage was covered with pus and fibrin, which extended over the defect and down into the granulation tissue. The cartilage on the borders of the defect was pale-staining, showing faint nuclei and evidences of having been penetrated by connective tissue. There was much fibrillation of this matrix. The cartilage in this area did not take the normal stain. It was in this region that there was evidence of a fibrous coat covering the cartilage, which had extended from the outer margins. This was the only evidence of a perichondrium. In the granulation tissue close to the bone margin was an island of old cartilage which took a pale stain and showed faint nuclei and evidence of having been penetrated by the granulation tissue. In the cartilage matrix, several wide breaks were present, which were due to the trauma. There was a proliferation of the fibrous tissue of the bone-marrow up into the defect. The bone itself took an extremely poor stain and looked necrotic. The picture again was undoubtedly due to the trauma plus infection.

EXPERIMENT 9—The knee joint was used, and the defects were made with the scalpel in the internal and external condylar ridges of the femur, the lower intercondylar space and the internal and external condyles of the tibia. The dog was killed four weeks after the operation.

Internal Condylar Ridge—The defect extended through the superficial layers. On gross examination, definite evidence of healing was found. The microscopic section was cut through the maximum point of the ridge. Over the whole ridge, there was a thick fibrous coat, which contained elongated fusiform cells. In places, the outer margin of this showed a cellular layer similar to the synovial membrane. It was not certain whether this fibrous layer represented a perichondrium or was a manifestation of repair. No definite cartilage cells were seen in its lower layers, as were sometimes seen when a perichondrium was present. The cartilage itself took a rather pale stain and showed fibrillation on the surface. Some of the superficial cartilage cells were well stained and had a distended quadrilateral appearance. It was thought that these might represent an early stage of new cartilage cells. The line of the calcified matrix was irregular, and in places it had been penetrated by a proliferation of connective tissue from the subchondral marrow.

External Condylar Ridge—The defect extended through the superficial layers. Gross examination showed some evidence of healing. The microscopic section was through the maximum point of the ridge. There was one small protrusion of cartilage, covered by fibrous tissue, which may have been a regenerative change. The edge of the matrix was slightly irregular and showed some disintegration.

The superficial cartilage cells were faintly stained. Some black detritus was observed along the surface. One margin of the cartilage was covered by a fibrous layer containing blood vessels, which was an extension of the capsule.

Lower Intercondylar Space—The defect was made through to the calcified matrix. Gross examination showed evidence of healing. The microscopic section was clearly cut through the defect. The defect had an irregular border on which the cartilage cells were of unusually large size. Superimposed on the cartilage margin was a layer of fibrous tissue, containing cartilage cells. This took a dark stain in places. At the terminal margin of the hyaline cartilage there was fibrous tissue containing cartilage cells and typical looking fibrocartilage. It was believed that this was normal for the marginal edge of the hyaline cartilage.

Internal Condyle of the Tibia—The defect extended through to the calcified matrix. Gross examination showed definite evidence of healing. The microscopic section was not cut through the defect and could not be included in the analysis. There was one rather interesting observation. On the edge of the hyaline matrix, adjacent to the fibrous tissue was a well circumscribed and well demarcated blood space, which looked like a venule within hyaline cartilage.

External Condyle of the Tibia—The defect extended through the superficial layers. Gross examination showed the defect to be well filled with fibrous tissue. The microscopic section did not show the area denuded. There was an extension of the fibrous tissue on one side over the hyaline matrix, which was the only evidence of a perichondrium. The most superficial layer of cartilage took a darker stain and contained elongated cells.

EXPERIMENT 10—The knee joint was used, and the defects were made with the scalpel in the patella, the external and internal condyles of the femur and the external and internal condyles of the tibia. The condylar ridges of the femur were traumatized by pounding with a metal hammer. The dog was killed four weeks after the operation.

Patella—The defect extended through the superficial layers. Gross examination showed evidence of healing. The microscopic section was clearly cut through the denuded area. Only the most superficial layers of cartilage were removed, about one fourth of the full thickness. There was a slight irregularity of the border of the defect. No new cartilage cells were observed. On one side, extending from the edge over the hyaline matrix for a short distance was a fibrous layer which contained some cartilage cells. This was the only evidence of a perichondrium. Along the margin of the matrix in one place, some elongated cartilage cells were seen, which were similar to a perichondrium.

External Condyle of the Femur—The defect extended through the superficial layers. Gross examination showed healing, with fibrous tissue attached. The microscopic section was cut through the defect. Along the margin of the incised cartilage, pushing the hyaline matrix out, were one or two large cartilage cells which were suspected of being new cartilage cells, but they did not take a deep stain and were not multinucleated. There was a great deal of debris along the margin of the cartilage. On one margin, the fibrous tissue from the synovial membrane extended over a portion of the hyaline matrix. This was the only evidence of a perichondrium. This fibrous layer had some cartilage cells in its lower portions.

Internal Condyle of the Femur—The defect extended through the superficial layers. Gross examination showed evidence of healing. The microscopic section

showed that about one half of the thickness of the cartilage had been incised. The margin of the incised cartilage was somewhat irregular with many faint-staining cartilage cells on the periphery. Along the superficial portion of the defect were some large quadrilateral cartilage cells which may have represented an early stage in the proliferation of new cartilage cells. On both lateral margins of the cartilage there was an extension of the fibrous tissue from the edges for a short distance. This fibrous layer contained some cartilage cells in the deeper parts. Blood vessels were seen in this perichondrium.

External Condyle of the Tibia—The defect extended through the superficial layers. Gross examination showed evidence of healing, which was more marked than in a similar area in the internal condyle of the tibia. The microscopic section showed that the defect reached through about one third of the thickness of the cartilage. The defect showed an irregular and indented margin of cartilage. There was some debris along the edge. The edge of the matrix in the defect showed some disintegration, with a proliferation of oval and spindle cells in some places. In the superficial layers, were a few large quadrilateral cartilage cells, deeply stained. These were thought to represent new cartilage cells. In the cartilage was a cleft in which there was granulation tissue containing some spindle cells. The fibrous tissue on one margin extended over the hyaline matrix for a short distance. This was the only evidence of a perichondrium.

Internal Condyle of the Tibia—The defect extended through the superficial layers (fig 2). Gross examination revealed definite evidence of healing. The microscopic section showed that the defect extended through about two thirds of the cartilage. In the defect there was a proliferation of fibrous tissue, which extended into the matrix in two nipple-like processes. Spindle cells were present in the outer portion of this and oval cells, of cartilage type, in the deeper portions. In this deeper part were some areas of hyaline matrix which were adjacent to a pale-staining and fibrillating hyaline matrix of the main portion of the cartilage. The impression was that the edge of the matrix showing the disintegration had been replaced with cartilage cells in fibrous tissue. This new tissue had arisen from the necrosis of the old cartilage. No new cartilage cells were observed. There was no evidence of a perichondrium.

External Condylar Ridge—The cartilage was traumatized with a hammer. Gross examination showed little evidence of the trauma. The microscopic section showed the maximum point of the ridge. The margin of the cartilage over the ridge was irregular, with indentations which contained fibrin, leukocytes and debris. A cleft extended down one half of the width of the cartilage. The calcified matrix beneath the ridge was broken in two places, and was irregular. In the cleft there was a proliferation of vascularized granulation tissue. Over the irregular margin of the cartilage, the cells were faint-staining, and the matrix showed some disintegration. Fibrous tissue extended over one margin of the cartilage for a short distance. This fibrous tissue was well vascularized. There was a proliferation of connective tissue from the bone-marrow up through the breaks in the calcified matrix. New cartilage cells were not observed.

Internal Condylar Ridge—The cartilage was traumatized with a hammer. Gross examination showed little or no evidence of the trauma. The microscopic section showed the maximum point of the ridge. In the matrix over the ridge were some oblique breaks. Over the maximum point of the ridge, the edge of the matrix was irregular. There was some fibrillation of this edge, with a few leukocytes attached. From the lateral margin of the ridge, extending over the matrix, was a thick fibrous layer which terminated at the maximum point of the

ridge Between these fibrous layers there was a protrusion of hyaline matrix and tissue The outward portion of this had the typical appearance of hyaline cartilage, with matrix and cells, while the inner and central portion had a fibrillar appearance with spindle cells Along the superficial margin of the cartilage were some lacunae which it was thought represented disintegrated cartilage cells The cartilage cells were generally well stained The protrusion of cartilage and fibrous tissue was believed to be a reaction to the trauma

EXPERIMENT 11—The knee joint was used, and the defects were made with the scalpel and the burr in the patella, the external and internal condyles of the femur, and the external and internal condyles of the tibia The condylar ridges of the femur were traumatized by pounding with a metal hammer The dog was killed two weeks after the operation

Patella—The defect extended through to the calcified matrix Gross examination was not made The microscopic section was not cut through the defect and could not be used in the analysis

External Condyle of the Femur (Outer Side)—The defect extended through to the subchondral bone No gross examination was made The microscopic section was not clearly cut through the defect Along the margin of the bone was some fibrocartilage which was covered by connective tissue Hyaline cartilage was not seen

Internal Condyle of the Femur (Outer Side)—The defect extended through to the subchondral bone No gross examination was made The microscopic section again was not clearly cut through the defect In connective tissue attached to the bone, a few cartilage cells were seen Hyaline cartilage was not found The connective tissue was well dotted with blood vessels

External Condyle of the Tibia—The defect extended through to the subchondral bone Gross examination was not made The microscopic section was clearly cut through the defect The defect did not contain fibrin or granulation tissue The edges of the cartilage on both sides showed some fragmentation, with fibrillation of the matrix The matrix and cells along this border both took a pale stain In places, the hyaline matrix had loosened from the calcified matrix This was probably due to the fixing and cutting of the section Over the hyaline matrix for a short distance on one margin there was a fibrous layer, which was the only evidence of a perichondrium The superficial edge of most of the cartilage showed elongated cells, which in places took a dark stain and resembled a perichondrium

Internal Condyle of the Tibia—The defect extended through to the subchondral bone Gross examination was not made The microscopic section was clearly cut through the defect The defect was well filled with granulation and connective tissue On one side of the defect, pale-staining cartilage projected into the granulation tissue The edges of this showed fibrillation and were intimately connected with the loose connective tissue Cartilage cells in the connective tissue extended from the projection of cartilage down into the defect Several pale-staining, disintegrating islands of cartilage were present in the granulation tissue on the superficial side The tissue in the defect was well filled with blood vessels The bone in places was faintly stained The palely stained edges of the cartilage and the connective tissue in the defect were in sharp contrast with the more heavily stained normal cartilage

External Condylar Ridge—The cartilage was traumatized with a hammer Gross examination was not made The microscopic section showed the ridge

clearly At the maximum point of this ridge, there was a break in the cartilage in its superficial portion In addition there were several other oblique breaks running into the matrix Fibrin was found in some of these clefts in the cartilage The edge of the matrix was irregular, with the cells and the matrix taking a faint stain There was one large piece of cartilage which looked as if it was about to be broken off The connective tissue of the bone-marrow had proliferated into the hyaline matrix in places On the outer margin of the cartilage was a short extension of fibrous tissue which contained blood vessels and was the only perichondrium present A dark-staining superficial layer of cartilage was seen in places, which was nonnucleated This appeared to be a perichondrium

Internal Condylar Ridge—The cartilage was traumatized with a hammer Gross examination was not made The microscopic section showed the traumatized area clearly Over the maximum point of the ridge, there was a depression in the matrix, which took a pale stain The matrix also showed fibrillation of the margin, and a break in the cartilage down toward the bone This was believed to be due to the trauma There was some cell detritus over the margin of the matrix in the traumatized area Fibrous tissue extended over the cartilage from the outer margin and terminated at the beginning of the traumatized area The lower portion of this contained some elongated cells that looked like cartilage cells This was the only evidence of a perichondrium

EXPERIMENT 12—The knee joint was used, and the defects were made with a scalpel in the patella, the external and internal condyles of the femur, the condylar ridges of the femur, the lower intercondylar space of the femur and the external and internal condyles of the tibia The dog was killed two weeks after operation

Patella—The defect extended through to the calcified matrix Gross examination was not made The microscopic section was clearly cut through the defect The margin of the defect was somewhat irregular and had some detritus adherent to it The cells along the margin were generally well stained In places, however, the matrix and the cells took a poor stain On one side of the incised area was a folded back piece of fibrous membrane which had long fusiform cells that looked like perichondrium, but this could not be traced over the margin of the cartilage The cells along the margin of the cartilage not in the defect were elongated There was an extension of a fibrous membrane over the margin of the cartilage from the edge for a short distance It was the only perichondrium present

External Condyle of the Femur—The defect extended through the superficial layers Gross examination was not made The microscopic section showed the incised area clearly This defect had a fairly regular margin and contained fibrin and leukocytes In places, the fibrin looked as if it was undergoing organization, there being some long fusiform cells present

There was considerable cell detritus between the fibrin and the hyaline matrix One budding cartilage cell along the edge looked as if it might be a new cartilage cell In places, the superficial cartilage layer was deeply stained and contained elongated cells parallel to the surface The synovial membrane was reflected for a short distance over the cartilage on one edge This was the only evidence of a perichondrium

Internal Condyle of the Femur—The defect extended through the superficial layers Gross examination was not made The microscopic section showed only the most superficial layers denuded This defect was small and the margin of the matrix was regular New cartilage cells were not present On one border

of the cartilage, a fibrous layer could be seen for a short distance, which contained blood vessels showing injection. This was the only evidence of a perichondrium. The defect contained a small amount of fibrin. Some of the cells and the matrix on the outer margin were faintly stained.

Condylar Ridges of the Femur—The defects extended through the superficial layers. No gross examination was made. The microscopic section showed the defects in both ridges clearly. The section was cut obliquely so that the cartilage of the epiphyseal line was continuous with the cartilage of the surface on the inner side. The edges of the defects were slightly irregular, with evidence of disintegration, and had some fibrin and débris adherent to them. In the cartilage matrix were some breaks which contained fibrin. The edges of the cartilage took generally a deeper stain and in places had a fibrillar appearance. This was not present over the maximum points of the ridges. There was a projection of fibrous tissue over the cartilage matrix on the edges for a short distance, it was the only evidence of a perichondrium.

Lower Intercondylar Space—The defect extended through to the calcified matrix. No gross examination was made. The microscopic section did not show the defect clearly. The section contained mostly cancellous bone. A few pieces of pale-staining hyaline cartilage were present on the surface of this bone. In places, the connective tissue on the outer border of the bone had penetrated the bone-marrow.

External Condyle of the Tibia—The defect extended through the superficial layers (fig. 1). Gross examination was not made. The microscopic section showed the defect clearly. The defect was fairly well filled with loose connective tissue and granulation tissue, which appeared to have proliferated in part from the fibrous tissue on one side of the defect. From the edge of the defect there was a proliferation of an area of new fibrocartilage which was surrounded by connective tissue. The cell columns in the deeper layers of cartilage on one side had definitely started to turn their lines of axis toward the defect. This gave them the appearance of leaning toward the defect. Considerable fibrin was seen in the granulation tissue. The edge of the cartilage in the defect took a faint stain and showed evidence of disintegration. Over the cartilage on one border for a short distance was an extension of the synovial membrane which was the only evidence of a perichondrium.

Internal Condyle of the Tibia—The defect extended through the superficial layers. Gross examination was not made. The microscopic section was cut to one margin of the defect and did not represent a true picture of the condition. The cartilage in no place looked like typical hyaline cartilage. Fibrils ran through most of it. There was one large area of fibrous tissue containing cartilage cells overlying an area of hyaline cartilage. This looked like a little hillock on top of the cartilage. None of the cartilage took a normal stain. There was no suggestion of a perichondrium.

EXPERIMENT 13—The knee joint was used, and the defects were made with the scalpel in the patella, the external and internal condyles of the femur, the upper intercondylar space of the femur and the external and internal condyles of the tibia. The condylar ridges of the femur were traumatized with a metal hammer. The dog was killed one week after operation.

Patella—The defect extended through to the calcified matrix. On gross examination, the denuded area looked unchanged. The microscopic section showed all the cartilage to have been removed from the patella, except small bits on either

margin There was no evidence of the formation of fibrin Fibrous tissue extended over the edges of the remaining hyaline matrix for a short distance

External Condyle of the Femur—The defect extended through to the calcified matrix Gross examination showed no change in the denuded area The microscopic section showed that only a small amount of hyaline cartilage was attached to the bone There was some formation of fibrin in one place Along the margin were a great many small sequestrations of cartilage and bone which showed evidence of disintegration and took a faint stain The edge of the hyaline cartilage was irregular, but took a good stain

Internal Condyle of the Femur—The defect extended through to the calcified matrix Gross examination showed no change The microscopic section showed an irregular margin to the defect in the calcified matrix The edge of the cartilage took a fainter stain than normal, and showed fibrillation Some fibrin was attached There were several small pieces of cartilage along this margin, and also some bits of cartilage with bone attached One of these had reattached itself to the calcified matrix with fibrin Over the cartilage for a short distance on one side was an extension of a fibrous membrane, which was the only evidence of a perichondrium

Upper Intercondylar Space—The defect extended through the superficial layers Gross examination showed no change in the denuded area The microscopic section showed the denuded portion The edge of this was unusually regular, but showed fibrillation and took a paler stain than normal Along the margin were some cartilage capsules, which had lost their nuclei Some debris was adherent to the surface

External Condyle of the Tibia—The defect extended through the superficial layers No change was observed in the defect on gross examination The microscopic section showed the incised area clearly There were some superficial cartilage cells which were distinctly larger and took a deeper stain than the normal ones Most of the margin of the cartilage took a lighter stain than normal These cells looked like new cartilage cells Some of the superficial cells appeared to have lost their nuclei and had only the capsule forms left on the margin There was one transverse cleft in the cartilage down to the calcified matrix, the borders of which showed some fibrillation

Internal Condyle of the Tibia—The defect extended through the superficial layers Gross examination showed no change in the defect The microscopic section was poorly stained and fixed There were so many artefacts that it was impossible to tell what were the true cartilage changes

External Condylar Ridge—The cartilage was traumatized with a hammer (fig 7) Gross examination showed a depression in the ridge made by the trauma The microscopic section showed the traumatized area clearly A depression in the cartilage over the maximum point of the ridge was filled with fibrin This fibrin also extended for a short distance over the margin of the cartilage on one side There were several clefts in the cartilage partially filled with fibrin The underlying calcified matrix was broken and depressed inward over the indentation on the margin of the cartilage The underlying bone also showed some fragmentation All these changes were believed to be due to the trauma The edge of the matrix was of a paler stain than the normal, and some of the cells showed evidence of disintegration This edge, however, was fairly regular Over one side of the cartilage for a short distance was a fibrous layer, which was the only sign of a perichondrium

Internal Condylar Ridge—The cartilage was traumatized with a hammer. Gross examination revealed evidence of the trauma. The microscopic section showed only the margin of the defect. The edge of the incised cartilage was irregular and faint-staining and had some detritus attached. Extending over one edge of the cartilage was a fibrous membrane, which was a perichondrium.

EXPERIMENT 14—The knee joint was used, and the defects were made with a scalpel in the patella, the external and internal condyles of the femur, the condylar ridges of the femur, the lower intercondylar space and the external and internal condyles of the tibia. The dog was killed one week after the operation.

Patella—The defect extended through the superficial layers. In the gross examination no change was noted. The microscopic section showed the defect clearly. The defect was not filled with fibrin. The edge was fairly regular, but the matrix and the cells took a lighter stain than normal. Along the cut margin were several large and deeply stained cells which were suspected of being new cells. There were some areas of a deeply stained, nonnucleated superficial layer of cartilage. On one edge the synovial membrane was reflected over the cartilage for a short distance, this was the only evidence of a perichondrium.

External Condyle of the Femur—The defect extended through the superficial layers. In the gross examination, no changes were seen. The microscopic section showed the denuded area to be well demarcated. There was an irregular margin, with some fibrillation and disintegration of the cartilage matrix. Along the surface, considerable debris and disintegrating cartilage cells were seen. The superficial layer of the cartilage in places was deeply stained, with small fusiform cells parallel to the surface. No perichondrium was present.

Internal Condyle of the Femur—The defect extended through the superficial layers. Gross examination showed no change. The microscopic section showed the defect clearly. The edge of the cartilage was fairly regular, with considerable debris or disintegrated cells along the margin. The superficial layers of the cartilage were slightly less stained than the underlying layers. The synovial membrane was reflected over the cartilage for a short distance on one margin, this was the only evidence of a perichondrium.

Condylar Ridges of the Femur—The defects extended through the superficial layers. The gross examination showed the defects unchanged. The microscopic section showed the defect in the external ridge to be well demarcated, but the defect in the internal ridge to be broken, owing to the poor preparation. Some fibrin and debris were seen along the borders of the cartilage, especially over the outer defect. The cartilage cells and matrix were generally well stained. Over the cartilage on one margin, for a short distance, was a proliferation of a fibrous layer which was the only evidence of a perichondrium.

Lower Intercondylar Space—The defect extended through to the calcified matrix. The gross inspection showed the defect to be unchanged. The microscopic section was cut below the defect in the popliteal space. The space between the condyles showed no hyaline cartilage. In this space, fibrocartilage was attached to the bone on one side, and cellular connective tissue, on the other. Some fibrin was present along the margins of the hyaline cartilage. On one border of the hyaline cartilage, there was a reflection of the synovial membrane for a short distance, which was the only evidence of a perichondrium.

External Condyle of the Tibia—The defect extended through the superficial layers. The gross examination showed no change in the defect. The microscop-

section showed the incised area to be fairly well demarcated. In this area were some fibrin and debris. In the cartilage was a break which showed a lighter staining matrix lining one side, with a scarcity of cartilage cells in this light matrix. There was a reflection of the synovial membrane for a short distance over the cartilage on one margin, this was the only evidence of a perichondrium.

Internal Condyle of the Tibia—The defect extended through the superficial layers. The gross examination showed no change in the incised area. The microscopic section was poorly cut and showed a great number of breaks in the cartilage. The margin of the defect was irregular and had some debris attached. The cartilage cells and the matrix were poorly stained. There was no evidence of a perichondrium.

DIABETIC GANGRENE

MEDICAL TREATMENT AND PROPHYLAXIS *

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ETIOLOGY

Exclude infection and trauma, and death from diabetic gangrene would disappear. At the New England Deaconess Hospital in the service of Dr. E. P. Joslin and myself, from January, 1923, to January, 1930, thirty-one deaths occurred in one hundred and eighty cases of diabetic gangrene or infection of the feet requiring amputation of the toes or legs. In only seven were the causes of death not directly due to infection. The spontaneous occurrence of gangrene, trauma or infection is as rare in the diabetic as in nondiabetic persons of a similar age. It therefore seems clear that although premature arteriosclerosis, differing somewhat from nondiabetic arteriosclerosis, is present in the diabetic patient, the frequency as well as the high mortality of gangrene are dependent on a specific diabetic factor which for lack of a better term I must call lowered resistance to trauma and infection due to the metabolic disturbance peculiar to diabetes, perhaps especially manifested in the skin. Another point of contrast appears in the relative rarity of severe infection in cases of thrombo-angitis obliterans in the nondiabetic person. Severe infections most commonly occur in patients with diabetes who have received inadequate treatment and whose condition therefore is not controlled. According to Campbell,¹ in animals that do not receive insulin suppuration often occurs after pancreatectomy, while in those given an adequate amount of insulin and food healing occurs by first intention. The paradoxical, yet I believe true, observation that diabetic patients with a given degree of infection or gangrene of the feet are on the whole somewhat better subjects for surgical treatment than nondiabetic patients is probably due to the fact that this specific diabetic factor can be brought under control by adequate medical treatment. It follows, therefore, that control of diabetes by appropriate treatment is of primary importance in the prophylaxis of gangrene and as the foundation for successful surgical treatment whether operative or non-operative.

* Submitted for publication, May 3, 1930.

¹ Campbell, quoted by Joslin. *Treatment of Diabetes Mellitus*, ed. 4. Philadelphia, Lea & Febiger, 1928, p. 770.

PATHOLOGY

The impairment of the blood supply to the feet by vascular disease is always a factor in diabetic gangrene. In legs amputated for gangrene this arteriosclerosis is characterized by the fact that although the arteries of the leg are of the muscular type, the changes found are predominately of the type which in nondiabetic patients is found in the elastic arteries, such as the aorta. In the legs of nondiabetic patients the changes consisting of calcification, necrosis and sclerosis, occurring chiefly in the media, form the so-called Monckeberg type of arteriosclerosis. No great narrowing of the lumen occurs until, through degeneration of the intima, a suddenly formed thrombus completely occludes the artery. Typical senile gangrene, usually of the dry type, then develops. Such senile changes may be present in the arteries of persons developing diabetes in the late middle life, and hence senile arteriosclerotic gangrene may occur in a diabetic person. Characteristically, however, in the arteries of diabetic persons there is found marked intimal involvement² consisting of a heaping up of intima with deposition of fatty material in which many cholesterol crystals are seen. The heaping up of intima results in an early and gradual narrowing of the lumen with a limitation in the amount of blood supply. This process is usually of slow development, but may progress fairly rapidly in the course of a few months. As a result of this slowly progressive occlusion of the lumen, there tends to develop a compensatory collateral circulation, so that in time in a foot in which the large arteries are partially or completely obstructed the blood supply may still be sufficient to keep the foot alive and in apparently satisfactory condition for the ordinary burdens of life. Gangrene develops when a sudden occlusion or thrombosis occurs for which the foot is not adequately prepared, or more frequently when the edema and inflammation, due to trauma or infection, cause thrombosis of small arteries. The infection spreads rapidly, due to the lack of resistance in the diabetic patient, and gangrene follows. Owing in part to the collateral circulation, diabetic gangrene is usually moist, and the foot frequently warm.

Calcification in the vessels of diabetic persons tends to develop at any age from youth upward and is favored by two factors: increasing age and increasing duration of diabetes. It occurs in other vessels, notably the aorta and coronary arteries, in many cases hypertension associated with arteriolar sclerosis in the kidneys, eyes and heart contributes to the final pathologic picture. The organ in which arteriosclerosis threatens life most frequently is the heart. In eighty autopsies at the Deaconess Hospital every patient over the age of 40 with diabetes of five years' duration had had sclerosis of the coronary arteries. The chief cause of death of patients with diabetic gangrene, with the excep-

tion of septicemia developing at the time of the gangrene, has been cardiovascular disease. Coronary thrombosis with infarction of the heart, recent or healed, occurred in 12 per cent of two hundred and eighty-two diabetic persons whose autopsies were studied by Warren³ and in 25 per cent of one hundred cases at the Deaconess Hospital. In treating patients who have diabetic gangrene, therefore, one deals with persons who have generalized arteriosclerosis, the extent and degree of which vary with the duration of the diabetes and the age of the patient, if the diabetes is uncontrolled, there is also a disturbance of metabolism which in some way reduces the resistance to infection. Yet the nature of the change in larger arteries affected by diabetes gives opportunity for an extensive development of a protective collateral circulation, which, barring trauma and infection, in time may become sufficient to prevent gangrene.

INCIDENCE OF GANGRENE

In the last four years, one in eleven diabetic persons over the age of 50 died of it as compared with one in eight dying during the preceding four years. The increasing longevity of diabetic patients brings more youthful persons into the arteriosclerotic zone. The average age of thirty-four persons with fatal diabetes in the hospital during 1929 was 63.5 years. The patients with gangrene are in reality much older than their chronological age, if one considers their extensive vascular disease and the duration of life after gangrene. Indeed, in the past it almost seems as if a year of diabetes added a year to a patient's true age. It should not do so in the future.

PREVENTION OF GANGRENE

The immediate causes of gangrene are preventable. On March 31, 1930, of seven patients in the New England Deaconess Hospital who had suffered amputations of legs or toes, three had cut corns without precautions. Clean hands and clean feet would have saved their legs. The fourth patient stepped on a nail and continued to work in spite of suppuration. The fifth and sixth had blisters produced by tight shoes. The seventh walked barefoot in zero weather striking his toe without remembering any injury, so deficient in sensation or so slight was the trauma that resulted in gangrene. Defective vision resulting in too deep cutting of corns, improper shoes causing trauma from pressure, unprotected feet and neglect of minor infections are causes that may be combated by the education of patients and by careful but energetic treatment by physicians.

The feet of diabetic persons are vulnerable because they are mechanically deformed. The feet of diabetic patients over 50 years of age are rarely free from obvious mechanical handicaps. Hammer

³ Warren. Pathology of Diabetes. Philadelphia: Lea & Febiger, 1930, p. 146.

TABLE 1—Data on Sixteen Patients Treated During 1929

Case Number,	Sex	Age	Weight, Lbs	Wassermann	Operations (Same Leg—This Entry)						Complications					Average Daily Diets								
					Minor Amputations			Major Amputations			Days in Hospital	Angina	Nephritis			Miscellaneous	Carbohydrate	Protein	Fat	Calories	Insulin			
					Date	Type	Anesthesia	Date	Type	Anesthesia			Nonprotein Nitrogen	Albumin	Blood Pressure									
6607	F	51	123	Neg	9	58	10/ 3/28	Amputation of 2 toes	Spinal	1/ 1/29	Amputation of lower part of leg	Spinal	115	0	39	vst	110	0	Preoperative 109 First week 77 Second week 82 Third week 88 Discharge 96	65 49 51 58 66	98 92 94 104 115	1,596 1,332 1,423 1,520 1,683	5 35 39 45 25	0.29 0.19
7781	M	68	160	Neg	1/4	6	5/ 7/29	Amputation of lower part of leg	Spinal	5/ 7/29	Amputation of lower part of leg	Spinal	21	0	27	opt	122	0	Preoperative 106 First week 101 Second week 131 Third week 150 Discharge 150	49 45 55 50 56	83 73 94 98 98	1,367 1,241 1,602 1,706 1,706	0 0 0 0 0	0.08 0.12 0.13
7707	F	62	108	Neg	5	1	2/ 9/29	Gritti Stokes	Spinal	2/ 9/29	Gritti Stokes	Spinal	52	0	27	vst	140	0	Preoperative 106 First week 90 Second week 108 Third week 108 Discharge 108	57 42 54 54 54	88 77 86 92 93	1,442 1,221 1,422 1,496 1,485	25 33 26 20 10	0.19 0.18 0.17 0.16
6926	M	61	123		20	1	5/11/29 5/23/29	Amputation of 2 toes Amputation of 1 toe	Spinal Spinal	6/ 4/29	Gritti Stokes	Spinal	18	0	56	st	120	0	Preoperative 91 First week 86 Second week 97 Third week 110 Discharge 114	52 29 50 55 58	84 58 79 82 103	1,328 982 1,299 1,398 1,615	15 31 20 18 5	0.20 0.18
6896	F	60	159	Neg	5/2	3.6	12/31/28	Amputation of 1 toe	Spinal	1/30/29	Gritti Stokes	Spinal	69	0		vst	120	Auricular fibrillation	Preoperative 104 First week 93 Second week 101 Third week 102 Discharge 108	51 39 39 43 44	65 56 61 62 61	1,205 1,032 1,109 1,138 1,157	0 10 10 10 10	0.20 0.29
7672	M	62		Pos	1/30+	3	2/14/29	Amputation of thigh	Spinal	2/14/29	Amputation of thigh	Spinal	31	0		vst	158	Tertiary syphilis and retinitis	Preoperative 101 First week 102 Second week 106 Third week 106 Discharge 106	63 65 66 66 66	85 108 113 113 113	1,421 1,640 1,705 1,705 1,705	30 31 20 20 20	0.12 0.17 0.18
7759	M	55	205	Neg	1/4	8-1	1/26/29 2/ 4/29	Amputation of toe and drainage Amputation of toe and drainage	Spinal Spinal	2/13/29	Gritti Stokes	Spinal	77	0	40	st	120	0	Preoperative 100 First week 100 Second week 100 Third week 103 Discharge 110	65 62 62 64 75	98 90 90 93 102	1,542 1,458 1,458 1,505 1,658	75 50 41 30 5	0.25 0.23 0.24 0.24 0.16

7780	I'	65	151	Neg	11	16	0	12/22/23	Gritti Stokes	Spinal	137	+	31	lt	180	Carbuncle of buttock	Preoperative first week	89	37	70	1,121	20	0.25
															100		Second week <th>85</th> <th>49</th> <th>79</th> <th>1,247</th> <th>45</th> <th>0.21</th>	85	49	79	1,247	45	0.21
																	Third week <th>98</th> <th>51</th> <th>83</th> <th>1,343</th> <th>35</th> <th>0.14</th>	98	51	83	1,343	35	0.14
																	Discharge <th>108</th> <th>53</th> <th>87</th> <th>1,427</th> <th>27</th> <th>0.11</th>	108	53	87	1,427	27	0.11
764	M	67	206		6	12	0	4/13/29	Gritti Stokes	Spinal	57	0	44	st	120	Chronic pulmonary tuberculosis	Preoperative First week	101	48	72	1,256	30	0.24
															80		Second week	87	32	78	1,182	47	0.23
																	Third week	95	50	81	1,309	27	0.20
																	Discharge	112	59	20	1,401	10	0.12
7809	I'	60	Neg	2/20	2		0	5/13/29	Gritti Stokes	Spinal	78	0	31	vst	175	0	Preoperative First week	59	36	55	875	0	0.18
															115		Second week	53	8	11	379	17	0.31
																	Third week	72	35	44	824	18	0.15
																	Discharge	74	27	58	926	10	0.17
6575	M	49	166	Neg	9	34	0	1/2/29	Amputation of lower part of leg	Spinal	103	0	vst		132	0	Preoperative First week	152	73	118	1,962	0	0.21
															81		Second week	152	73	118	1,962	10	
																	Third week	152	73	118	1,962	5	0.11
																	Discharge	162	76	118	2,026	0	0.15
7834	I'	59	118	Neg	7	3	0	4/1/29	Gritti Stokes	Spinal	58	0	32	vst	140	0	Preoperative First week	95	55	80	1,320	50	0.20
															50		Second week	97	54	80	1,324	61	0.20
																	Third week	96	70	80	1,304	11	0.20
																	Discharge	97	49	80	1,304	20	0.20
7619	I'	50	124	Neg	9	3	0	3/7/29	Gritti Stokes	Spinal	40	0	spt		140	0	Preoperative First week	94	55	83	1,388	27	0.22
															50		Second week	88	33	53	1,069	38	
																	Third week	91	43	81	1,265	31	0.21
																	Discharge	93	51	83	1,380	28	
8005	I'	65	108	Neg	5	10	0	5/21/29	Amputation of thigh	Spinal	53	0	17	spt	160	0	Preoperative First week	92	43	81	1,289	0	0.18
															71		Second week	97	43	72	1,208	15	0.16
																	Third week	115	55	83	1,427	21	0.12
																	Discharge	121	61	90	1,550	12	
8011	I'	75	165	Neg	6	6	0	5/29/29	Amputation of thigh	Spinal	40	+	33	spt	136	Auricular fibrillation	Preoperative First week	81	79	88	1,284	0	0.22
															51		Second week	81	33	69	1,077	23	0.22
																	Third week	102	43	91	1,426	21	0.17
																	Discharge	95	48	97	1,355	10	
8264	I'	66		Neg	16	65	0	7/7/29	Amputation of thigh	Spinal and ethylene	78	+	35	spt	100	Aortic coronary thrombosis at onset of angina pectoris	Preoperative (one meal) First week	44	10	26	458	0	0.13
															70		Second week	96	26	52	956	0	0.09
																	Third week	102	11	50	1,391	0	0.11
																	Discharge	130	46	81	1,440	0	
																	(house diet)	163	65	88	1,724	0	0.11
Average	0	61			50				Preoperative First week						99		First week	99	73	81	1,359	19	0.21
																	Second week	91	12	71	1,101	28	0.20
																	Third week	103	51	86	1,389	23	0.17
																	Discharge	108	51	89	1,455	18	0.17
																		120	59	96	1,585	7	0.17

improvement even of patients with gangrene is far greater than was supposed. At present (August, 1930) most patients receive 150 Gm of carbohydrate before discharge.

So striking are the changes in dietary treatment from one period to another that it is obvious that still greater improvement may occur. Some definite information regarding the best diets in cases of diabetic gangrene is desirable. Before operation, the existence of fever and the generally disturbed state of the patient require the use of the simplest food in amounts which the patient can retain. After operation, however, the problem of determining the optimal diet arises. The basal metabolism in cases in which toes or legs have been amputated as compared with the total calories of the diets is shown in table 3. In

TABLE 3—*Postoperative Basal Metabolism of Eleven Diabetic Persons*

Case Number	Sex	Age	Activity at Time of Test	Date	Calories in Diet	Deviation from Standard, per Cent	Pulse	Computed Calories per 24 Hours	Weight, Pounds	Period Since Operation	Operation	
											Amputations	Other
5155	M	45	Normal	4/ 3/26	1,576	- 4	80	1,829	194 $\frac{1}{4}$	24 years	2 legs*	
4396	M	63	Bed	1/28/25	1,596	+10	67	1,441	135	33 days	1 toe	
4396	M	63	Chair	4/ 5/26	1,561	+ 7	88	1,320	114	23 days	1 leg	
4396	M	63	Walking	4/26/26	1,553	+25	74	1,549	114	46 days	1 leg	
5186	M	60	Bed	4/ 5/26	1,751	+12	88	1,390	116 $\frac{3}{8}$	14 days	2 legs	
5163	M	59	Chair	4/ 5/26	1,568	- 2	76	1,223	118 $\frac{3}{8}$	23 days	1 leg	
5250	M	60	Bed	4/ 8/26	1,748	+40		1,355	90 $\frac{1}{2}$	47 days	2 legs	
6643	F	62	Chair	2/ 3/28	1,369	- 1	64	1,035	92	67 days	1 toe	
4420	M	65	Chair	2/ 4/28	1,927	+22	78	1,963	176 $\frac{1}{4}$	18 days	1 toe	
6088	M	68	Bed	2/ 8/28	1,587	+ 1	60	1,211	122 $\frac{3}{8}$	30 days		Carbuncle
6656	M	67	Bed	2/14/28	1,898	+19	92	1,575	135 $\frac{3}{8}$	27 days	1 leg	
6648	F	61	Bed	2/15/28	1,505	+25	76	1,461	114 $\frac{1}{2}$	21 days	1 toe	
6790	M	61	Bed	2/16/28	1,686	- 7	68	1,174	121 $\frac{3}{4}$	24 days	1 toe†	

* Amputations below the knee at the age of 21.

† Gritti Stokes amputation on March 19, 1928.

case 5155 the patient was not convalescent, he was in the hospital only a few days, and a comparison of his diet and his computed metabolism is not proper. His data are included to show that the basal metabolism of a legless diabetic patient, uninfluenced by the effects of a recent infection or operation is about 21 calories per kilogram of body weight. Three determinations of the metabolism in case 4369 showed some variation. The first test was done before the patient's leg was amputated. The second test was done a year later, when he had lost some weight. With a total loss of 21 pounds (9.5 Kg.), the loss in metabolism was but 121 calories. In the third test the metabolism was so much higher as to seem aberrant but there was no reason to doubt it. In case 5250 both legs were amputated through the thigh because of gangrene and severe infection. The patient was extremely emaciated but was not nervous and did not have a severe case of diabetes. His high metabolism was probably due to the persistence of slight infection.

in his wounds. The average deviation of the group from the Harris and Benedict standard predicted metabolism was ± 12 per cent. The average twenty-four hour computed calories was 25 per kilogram of body weight. When one considers the lowering of the metabolism during sleep, which might compensate for the slightly increased metabolism associated with movements in bed, it is probable that most patients with gangrene when free from active infection will retain their weight if given sufficient food to supply 25 calories per kilogram of body weight. For certain emaciated or debilitated patients, additional food might be necessary. The caloric needs of persons must be estimated not only from computations but after some consideration of their physical make-up, appetite and indications shown by their progress from day to day. The composition of the diet will also depend on complications such as nephritis and also on variations in the caloric tolerance of the

TABLE 4—*Diet Before Operation*

Food	Break fast	Dinner	Supper	Total, Gm	Carbo- hydrate	Protein	Fat
5% vegetable		150	150	300	10	5	
10% vegetable		75	75	150	10	3	
Orange		150	150	300	30		
Oatmeal	30			30	20	5	2
Uneda	2	2	2	6	30	3	3
Potato		60		60	12	2	
Egg	1			1		6	6
Cream, 20%	60	30	30	120	4	4	24
Butter	10	15	10	35			29
Meat		60		60		32	20
Grapefruit	200		200	10			
Grams					126	60	84
Calories					4	4	9
Total calories, 1,500					204	240	756

patients. Rapid changes in the amount of carbohydrate in the diet may be made as tolerance improves, as shown in table 1, and more surely if the intake of fat is restricted.

Preoperative Treatment—A liver well stored with glycogen is the diabetic person's best protection during an operation. He must therefore receive sufficient carbohydrate, but under such conditions that he will surely utilize it. The diet to be used before operation depends on the length of time available for preparation. In an emergency operation to be performed within a few hours of the patient's admission to the hospital, because of threatening sepsis, no attempt should be made to force foods. It is worth while, however, to have the patient receive about 20 Gm of carbohydrate in the form of 200 Gm of orange juice or oatmeal gruel, made from 30 Gm dry weight, with insulin. When a period of days elapses between the admission and the operation the patients should receive a diet of approximately 100 to 150 Gm of carbohydrate with 1 Gm of protein per kilogram of

body weight and sufficient fat to give 25 calories per kilogram of body weight. Such a diet for a man weighing 132 pounds (59.9 Kg) is shown in table 4.

If the urine contains sugar, and especially if diacetic acid is present, insulin should be given as soon as the patient is admitted to the hospital or as soon as the diagnosis of diabetes is established. If sugar and diacetic acid are present, it is usually proper to start with 10 units three times a day, provided sugar is present in the urine before every meal. If the urine becomes free from sugar, the insulin should be reduced to 5 units before the next meal, if the next specimen of urine is free from sugar, the dose should be omitted. At the time of operation it is rarely necessary to give insulin during the actual operation, two or three hours before, my associates and I usually give 15 Gm of carbohydrate in the form of 150 cc of orange juice and 10 or 15 units of insulin, unless the patient is accustomed to much larger doses. Even then, it has not been necessary to use more than 20 units before operation.

Postoperative Treatment—Vomiting rarely occurs after operation. If spinal anesthesia has been used, the patient can begin taking food immediately. In cases in which general anesthesia is followed by vomiting, hypodermoclysis of 1,000 cc of 5 per cent dextrose solution in physiologic solution of sodium chloride or an intravenous injection of 500 cc of 10 per cent dextrose solution in physiologic solution of sodium chloride may be used to replace fluids, give nourishment and check the nausea.

The usual diet is simplified by the use of more concentrated foods, such as cereal, potato, rice and toast, in such quantities that the total amount of carbohydrate in the diet is unchanged. The urine is tested every four hours, and the insulin is given according to the amount of sugar present. If the urinary test is red or orange with Benedict's solution, then 15 units of insulin may be given, if it is yellow, 10 units, if green, 5 units. The order for insulin is written contingent on urinary tests, so that unnecessarily large doses of insulin will not be given as a routine after the patient becomes free from sugar during the two or three weeks following amputation. If the urine becomes sugar-free, additions of 10 Gm or more of carbohydrate to the prescribed diet may be made from day to day to keep pace with the growing carbohydrate tolerance. Gains in tolerance depend on the removal of infection, the constancy and regularity of the diet, the use of insulin and perseverance in seeking to increase the portion of carbohydrate in the diet. The use of exercises in bed improves both muscles and morale. They are begun within a few days after the operation, provided the patient is free from a high temperature. At first they consist only of breathing exercises and of motions of the arms. Gradually the number of exercises are increased and the remaining leg shares the

exercises Hand elastic exerciseis are attached to the foot of the bed, so that the patient may exercise more vigorously as he gains in strength

Use of Dextrose Solutions—For patients in a state of shock or so weakened that they cannot take food by mouth, the use of dextrose given by rectum, subcutaneously or intravenously, is of great value Rectal injections can be used but a few times because of the irritability of the rectum Dextrose given intravenously is rarely needed when spinal anesthesia has been used However, in some cases it is of great value as a means of getting nutrient substances into the body and as a stimulant to the circulation Ordinarily, it is given in 10 per cent solution in amounts of from 500 to 1,000 cc once or twice a day Precautions must be observed in its use owing to the fact that, when insulin is given with dextrose and little other food is being taken, hydroglycemia may follow a few hours after injections Hypoglycemia seems to be caused by a stimulation of the pancreas by the dextrose When a patient is being fed exclusively by intravenous injections of dextrose solution, orders for the administration of insulin should be so written that insulin cannot be given unless a test of the urine is made, and unless the dose is adjusted according to the presence or absence of sugar in the urine

Laboratory Aids—A blood culture should always be taken when the patient has gangrene and fever If septicemia is suspected, the absence of sugar in the urine is usually strong evidence against its existence, and this may be a decisive point in deciding the type and the time of operation The absence of sugar in the urine must never be taken as proof of the absence of diabetes, since the dextrose threshold in the blood is often elevated in persons with diabetes of long duration and in older diabetic persons If hyperglycemia is found, the surgeon is thereby warned that vascular disease in the extremities is probably of the diabetic rather than of the purely senile type, and that diabetic treatment may be valuable and even life-saving Such patients may develop dangerous acidosis and even coma after operation if precautions are not taken Diacetic acid should always be tested for by means of the ferric chloride reagent whenever the urine is examined for sugar Only in this way can the surgeon or the physician recognize the development of acidosis in its earliest stages

Blood Sugar—Variations in the blood sugar are the most valuable single indication of variation in the diabetic metabolism When the amount of blood sugar is between 0.1 and 0.15 per cent, the patient is for the time secure from acidosis and hypoglycemia The higher the amount of blood sugar before operation, the more serious is the general condition of the patient and the worse the prognosis (table 5) There is no level of blood sugar, however, which necessarily makes the case hopeless The highest amount of blood sugar is found in severe aci-

dosis, and a figure above 0.4 per cent in a surgical case should always suggest approaching coma, whether before or after operation. In many cases of long duration, with advanced arteriosclerosis and acidosis, the lower the amount of sugar in the urine the higher the amount of sugar in the blood. Anesthesia produces elevation in the blood sugar, the greatest change being caused by ether, the next greatest by nitrous oxide and the least by ethylene. Insulin reduces the sugar in the blood at a rate which varies somewhat with the severity of the diabetes, the presence of infections, the size of the dose of insulin and the previous diet of the patient. The maximum lowering of the blood sugar after a dose of insulin is found from three to six hours after the injection. It is almost impossible to predict with certainty the amount of lowering of the blood sugar that a given dose of insulin will cause. In diabetic persons

TABLE 5—*Duration of Life of Patients Surviving Amputations of Toes or Legs Between Jan. 1, 1923 and Jan. 1, 1928 Compared with the Percentage of Sugar in the Blood*

Blood Sugar, per Cent	Patients	Gangrene		Average Duration of Life, Dead	
		Living, August, 1929			
		Number	Years	Number	Years
0.30 to 0.45	14	6	2.2	8	1.2
0.20 to 0.29	44	22	2.6	22	1.2
0.10 to 0.19	20	8	3.2	12	1.1
<i>Infection</i>					
0.30 to 0.45	9	3	2.0	6	0.8
0.20 to 0.29	18	14	2.1	4	1.9
0.10 to 0.19	19	8	3.8	11	1.1

changes occur from hour to hour. The diet and insulin must be adjusted daily, even hourly, in emergencies, according to the urinalyses or blood tests.

Reactions to Insulin—Hypoglycemic reactions are serious, and are to be avoided at all costs. They endanger the patient's life, because they threaten his diseased heart. The symptoms of hypoglycemia are weakness, severe hunger, tremor, convulsions or unconsciousness usually occurring from three to eight hours after a dose of insulin. Queer mental states or absolute unconsciousness may develop with slight or no warning. The prevention of hypoglycemic reactions depends on constant watching of the urine, the diet and the blood sugar, especially in patients having less than their usual diet or receiving dextrose solution intravenously. It is wise to test the blood sugar at those times in the day when hypoglycemia is most likely to develop, namely, at 11:30 a. m., 4:30 p. m. or 9 p. m. If the urine of a patient given insulin three times a day is tested every six hours and is found to be sugar-free once in the day, that is the time when hypoglycemia is most likely to occur. If the blood sugar level is found to be below 0.1 per cent at this time, it is well to reduce the dose of insulin from that

given four hours before, even though no symptoms have been recognized, or else to have the patient take 10 Gm of carbohydrate in the form of orange juice or two Uneeda crackers. Before the patient's discharge from the hospital, the blood sugar test should be done at 11 30 a m or 4 30 p m in order to avoid the occurrence of hypoglycemia at home.

Treatment for hypoglycemia should be instant. In mild cases, 100 cc of orange juice may be given by mouth. When this fails or the patient is unconscious, dextrose solution (20 cc of a 50 per cent solution) should be injected intravenously. The hypodermic injection of 0.5 cc of epinephrine (1:1,000) sometimes brings the patient to, so that he can take orange juice or Karo syrup.

Acidosis—In every case of gangrene coma is likely to occur. If the patient vomits, becomes drowsy or has pain in the abdomen, coma should be considered first, and the urine should be tested for sugar and diacetic acid. When diacetic acid is present in the urine, a carbon dioxide-combining power in the blood plasma of from 35 to 50 per cent by volume means mild acidosis, when the percent is below 20, the patient is usually in obvious coma. The onset of coma is insidious, with loss of appetite, nausea and pain in the abdomen. Air hunger is a late symptom. Treatment with insulin should begin long before air hunger develops, and should be as promptly and energetically carried out as would be treatment for intra-abdominal hemorrhage. Gastric lavage, an enema and subpectoral infusion of saline are essential. From 10 to 25 units of insulin hourly or even half hourly is usually necessary until glycosuria is controlled.

Complications—Arteriosclerotic disease of the heart and kidneys far exceeds all other complications. Most important is the protection of the skin against boils and carbuncles and of the feet against pressure sores. Scrupulous cleanliness of the skin, use of nonirritating soap and frequent changes of position to avoid the macerating effect of pressure and perspiration help to prevent carbuncles in obese patients. When small furuncles appear, ultraviolet treatment is valuable. All patients who have had a leg amputated should have a thick clean woolen sock on the other foot to avoid pressure of the heel against the bed. A Balkan frame over the bed with hand grips hung from the frame makes it possible for a patient to use his arms to turn instead of digging his heel into the bed for this purpose.

PROGNOSIS

The prognosis for patients with lesions of the feet depends on (1) the nature and severity of the infection, (2) the condition of the blood supply of the foot and (3) the opportunity for adequate treat-

ment for the diabetes and complications. All lesions of the lower extremities in the diabetic patient are classified etiologically as chiefly due either to infection or to a deficient blood supply. Patients whose condition is primarily due to infection usually have warm feet and palpable dorsalis pedis pulse, patients with deficient circulation usually have no pulsation in the dorsalis pedis artery and cold feet. A more complete discussion of this classification is given in an article by Dr L. S. McKittrick. The two groups differ in many respects. The average age of patients in the infectious group was 58.8 years, and the duration of the diabetes 8.5 years. The average age of those in the circulatory group was 63.5 years, and the duration of the diabetes 7.5 years. The prognosis in the two groups differs widely, and in discussing various factors concerned with prognosis in diabetic gangrene the cases should be grouped under these two headings.

The thirty-one deaths occurring in the hospital illustrate the four most unfavorable prognostic criteria: (1) virulent infection in feet with absent dorsalis pulsation and a deficient blood supply (twenty-five belonged to the circulatory group), (2) advanced age, the average being 69 years, (3) long duration of diabetes, the average being 8.9 years, (4) angina pectoris and chronic nephritis. Four deaths from coronary thrombosis in cases of the gangrene group are more impressive when included with six deaths in this group occurring within a year after operation. A history of angina pectoris is easily missed. The pressure or pain over the sternum may be slight, but if it bears a definite relationship to exertion or nervous excitement, the diagnosis cannot be doubted. Electrocardiograms often give definite evidence of marked myocardial change, presumably secondary to coronary disease, even when attacks of angina have not occurred. Sudden death is an imminent possibility in any diabetic person after 60 years of age.

In contrast to the patients who died in the hospital are thirteen patients with gangrene living an average of 4.2 years after operation. Their average age was 59 years as compared with the average of 63.5 years for all cases of gangrene. The average duration of the diabetes was 5.2 years in contrast to an average duration of 8.5 years for the entire group. The average amount of blood sugar was 0.2 per cent and the average amount of sugar in the urine on admission was 0.4 per cent. In four cases the systolic blood pressure was above 150, and on only one occasion was it under 110. In no case was the nonprotein nitrogen above normal, and in no case was there suggestive evidence of severe coronary disease. The infectious group, in which the average age was 60.2 years and the average length of life 4.3 years after operation, consisted of five males and two females. The average duration of diabetes was 5.9 years as contrasted with a duration of 7.5 years in the entire group of infectious cases. In four cases of this group

amputation of the toe was performed and in three amputation of the leg. Again, the average amount of blood sugar was 0.2 per cent and the average amount of sugar in the urine 1.1 per cent. In two instances, the nonprotein nitrogen was above 40 mg per hundred cubic centimeters. In no case was angina pectoris present. Younger patients with diabetes of shorter duration, the absence of septicemia and advanced coronary disease are the reasons for a better prognosis.

The prognostic value of the purely diabetic factors is paradoxical. The more severe the disturbance, the greater the relief that will be afforded by adequate and successful treatment. The level of the blood sugar and the amount of sugar in the urine on admission to the hospital are not closely related to the ultimate prognosis, owing to the fact that they may be influenced so markedly by treatment during the week or two preceding admission. Much more important than the level of blood sugar at the time of admission are the course and treatment of the diabetes during the preceding five or ten years. It is true, however, that an excessively high blood sugar has a somewhat unfavorable significance, as seen from table 5.

In general, the level of the blood sugar is so much influenced by infection and the presence or absence of recent treatment that its chief value is as a guide to diabetic treatment.

The blood pressure is of no outstanding importance in relation to prognosis. In 50 per cent the systolic blood pressure exceeded 150 mm. Hypotension with a systolic pressure below 110 occurred in only six cases. So far as a preexisting hypertension may have paved the way for coronary disease or chronic nephritis it is of importance, but at the time of treatment in the hospital the level of the blood pressure seemed to have little bearing on the outcome. Actual cardiac failure with decompensation has occurred in only two cases in the hospital.

The only two cases in which gangrene developed, in spite of fairly good care of the feet, were cases associated with angina pectoris and chronic myocarditis.

EXPLOSIONS OCCURRING DURING THE USE OF ETHYLENE *

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A few months after Luckhardt and Carter had published their articles on the original clinical work with ethylene, Brown¹ reported the results of an extensive investigation concerning the explosibility of ethylene mixtures. In this paper, he mentioned the places where explosion may occur as

(1) While the gas is compressed in the cylinder, (2) after emerging from the cylinder but not mixed with oxygen, (3) in the mixing chamber or distributing apparatus mixed with oxygen and (4) after escaping into the room through the valve in the facepiece

In the first two locations one is presumably dealing with the pure gas, and whether or not explosions can occur at these points depends on the inherent character of the gas. In order to settle this question definitely, one must know whether it is possible to cause the pure gas to explode or whether it can explode spontaneously. Some gases, such as acetylene, are unstable when highly compressed. Does ethylene show such properties? Experience has shown that ethylene is not unstable when under high pressure, and that the pure gas cannot be made to explode. Brown¹ has shown that ethylene unmixed with oxygen will not explode, and, furthermore, that explosions do not occur in mixtures of ethylene and oxygen unless at least 40 per cent of the mixture is oxygen. This work was confirmed by Hornor and Gardener,² although their results show that ethylene oxygen mixtures containing a minimum of 30 per cent of oxygen may explode. The criterion, however, established by these workers was rigid. If the mixture was not exploded at once by a spark, a continuous arc was passed through it for one minute before it was definitely said to be nonexplosive.

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~ From the University Hospital, Ann Arbor, Mich

1 Brown, W E Explosibility of Ethylene Mixtures, J A M A 82 1039 (March 29) 1924

2 Hornor, A P, and Gardener, C B Anesth & Analg 7 69 (March) 1928

Additional evidence showing that pure ethylene or very concentrated mixtures of the gas are not explosive is found in the observation of Herb³ that following an explosion in the distributing portions of the anesthetic apparatus, there is no tendency for the explosion to flare back into the machine or up to the tanks. On several occasions the pure gas coming from the tank was ignited, but the flame could be easily extinguished. Moreover, we must remember that although the use of ethylene by the medical profession is recent the gas has been known to chemists and used in industry for many years. If the pure gas were unstable or if its use were fraught with danger of mishap, warnings of these dangerous properties would have been forthcoming. The fact that many thousand drums of the highly compressed gas have been shipped to all parts of the country without accident argues well for its stability.

Recently a terrible accident occurred in an Indiana hospital⁴. A physician working with a gas machine carrying tanks of oxygen, nitrous oxide and ethylene was killed when a violent explosion occurred. The accident was reported in the papers as due to an ethylene explosion. Subsequent investigation proved that the tank of nitrous oxide and not the ethylene tank had blown up. That matter is of secondary importance, however, to the fact that the tragedy proved the extreme instability of mixtures of nitrous oxide and ethylene under pressure. In gas machines of the older type, when the valves on the tanks are not tightly closed, contamination of certain tanks with gases from other tanks on the same machine may occur. The fact that mixtures of nitrous oxide and ethylene in certain proportions may be extremely explosive has not been sufficiently emphasized. Circulars informing the medical profession of this danger and also mentioning the possibility of the gases mixing in the tanks when attached to certain old style machines were sent out by a chemical supply house to users of their products. Hewer, in two publications,⁵ mentioned the fact that ethylene forms explosive mixtures with both oxygen and nitrous oxide. Hornor and Gardener² showed that mixtures of nitrous oxide and ethylene are explosive when the latter gas is present in concentrations of from 5 to 35 per cent. Above concentrations of 35 per cent ethylene, explosions do not occur. Thus we see that small amounts of nitrous oxide in ethylene will not lead to explosion but that small amounts of ethylene in a nitrous oxide tank

³ Herb, I. C. Explosions of Anesthetic Gases, *J. A. M. A.* **85** 1788 (Dec 5) 1925

⁴ Personal communication to Dr. Cabot

⁵ Hewer, C. L. *Lancet* **1** 173 (Jan 24) 1925), *Brit. J. Anaesth.* **3** 174 (April) 1926

may be very dangerous. On this basis alone, we can understand why it was that a nitrous oxide tank and not an ethylene tank blew up in the recent accident in Indiana.

In view of all the evidence that has accumulated on the subject it seems that pure ethylene will not explode either when ignited as the free gas or spontaneously when compressed in steel cylinders.

Since it is clear that the pure gas does not explode, all the operating room accidents that have occurred with ethylene must have been due to the ignition of mixtures of ethylene and oxygen in the mixing chamber of the machine, in some distal portion of the apparatus, or out in the room after the gas has been exhaled by the patient. Before considering explosions occurring in these different places, we must ask ourselves an important question.

Can mixtures of ethylene and oxygen explode spontaneously? Chemical mixtures are known that are so exceedingly unstable that an explosion may occur with no apparent cause. Other mixtures may explode if some slight chemical or mechanical stimulus is provided. Sise⁶ stated that mixtures of ethylene and oxygen under high pressure, as would be true if ethylene should leak into an oxygen tank, may explode spontaneously. The recent disaster in Indiana proved the same thing to be true of mixtures of ethylene and nitrous oxide. However, it is fairly evident that at normal pressures even the most explosive concentration of ethylene in oxygen will not blow up in the absence of a definite exciting cause. A great deal of experimental work has been done, employing low concentrations of ethylene in oxygen without accident, and during practically every ethylene anesthesia, especially toward the end when the patient is flooded with oxygen, the concentration of the gases must at some time be at the optimum point for explosion to occur. Moreover, the gases are not stationary but are passing fairly rapidly through a closed system, being thereby subjected to mild traumatic influences. The most satisfying argument against the theory of spontaneous explosion, however, is found in the fact that for all the explosions that have occurred a tangible exciting cause can be found. The cause has been either actual flame or cautery near the anesthetic apparatus or in many cases a static spark occurring either inside the machine and distributing hoses or out in the operating room. Explosions occurring outside of the machine will be considered first.

EXPLOSIONS OCCURRING IN THE OPERATING ROOM

Brown,¹ in his early report on the explosibility of ethylene mixtures, concluded that explosion due to gas that had escaped into the

6 Sise, L. F. Boston M. & S. J. **192** 287 (Feb 12) 1928

room was a negligible possibility. He based his view on a theoretical calculation which showed that in the average-sized operating room and with average pulmonary ventilation by the patient six hours would be required before the concentration of ethylene in the room could reach the explosive level of about 5 per cent. He assumed no ventilation in the room, a factor usually always present to a variable extent. He also assumed uniform diffusion throughout the room, while in reality, since the gas is but slightly lighter than air, it probably diffuses slowly and forms currents or strata much like those formed by tobacco smoke in a still room. Under these conditions it is possible to understand how an explosion could occur. Davis⁷ and Carne⁸ reported explosions occurring in the room some distance from the patient and the gas machine, and Sise⁶ commented on the possibility that exists for such accidents to occur.

It is obvious that the mere presence of even highly explosive mixtures of ethylene and oxygen in the operating room will do no harm, provided no agent is present that may ignite the gases. The explosions that have occurred during the use of the cautery might well have been caused by careless use of roentgen equipment, a spark produced on the brushes of an electric motor or a spark produced when an electric circuit of any sort is opened. These are perfectly evident sources of danger not only with ethylene but with ether as well. Sparks caused by electrostatic charges may be equally dangerous. They are, as a matter of fact, a much greater hazard than the obvious things, not because every static spark means an explosion but because they belong to a world unseen and may be generated in so many different ways. A static spark always results and can be produced only when two bodies of different electrostatic charges are separated or brought together. The charge must always be present before the spark and, unfortunately, nature has not given man the sense organ that can perceive when objects about us are charged. To combat such a situation we must adopt indirect methods and fall back on our knowledge of the fundamentals of electrostatics. A consideration of this matter in detail will be found later in this paper.

To eliminate the danger from explosions occurring out in the operating room, two possibilities must be considered. The explosive gases can be prevented from getting out in the room where they might be ignited, or measures can be taken to remove from the operating room any possible source of ignition. The latter method is the one

7 Davis, C. H. Explosibility of Ethylene, *J. A. M. A.* **82** 1607 (May 17) 1924.

8 Carne, A. M. *Anesth. & Analg.* **3** 104 (June) 1924.

usually adopted. Use of the cautery or any apparatus through the action of which a spark may be produced is strictly prohibited in the operating room where ethylene is employed. The weak point usually found in this method is that precautions against static spark are not taken and sooner or later an explosion occurs. Ethylene is blamed for the trouble (which might have occurred with ether vapor as well), and its use is curtailed. Means for eliminating the hazard of static spark in the operating room will be considered later.

The other method of preventing explosions in the operating room is to prevent ethylene from entering the room either by the use of a hose connecting the exhaust valve of the facepiece to the outside or by the use of a closed system. Salzer⁹ described a system of the first type. He uses an attachment which fits over the expiratory valve of the McKesson facepiece. To this device is connected a noncollapsible tube leading to the outside. The arrangement is simple and easily installed, but to be sure that it accomplishes its purpose, leakage of gases around the cushion on the patient's face would have to be prevented.

The system of rebreathing described by Gatch¹⁰ is used exclusively by some anesthetists, and if the rebreathing is complete, the amount of gas escaping into the room is said to be insignificant. Poe¹¹ used such a system in a series of 8,884 ethylene cases with great satisfaction and without mishap. He employs the Sander's modification of the Gatch apparatus, which has been used in approximately 185,000 administrations of ethylene in Texas and other states without an explosion occurring.

A strictly closed system in which the respiratory carbon dioxide is absorbed in soda lime, and oxygen and the anesthetic gas are admitted in small quantities as needed provides a means whereby no ethylene (or other gas) can get out into the operating room. This type of equipment has been used on the continent for the administration of acetylene, and it possesses the disadvantages of being both cumbersome and expensive. It should be pointed out, however, that the closed systems and, to a lesser extent, administration with rebreathing allow the use of considerably smaller quantities of the anesthetic agent. In the closed system the same ethylene could be used over and over

9 Salzer, M. Method of Eliminating Danger of Explosion in Use of Ethylene, *J A M A* **88** 315 (Jan 29) 1927.

10 Gatch, W D. The Use of Rebreathing in the Administration of Anesthetics, *J A M A* **57** 1593 (Nov 11) 1911.

11 Poe, J G. *Anesth & Analg* **7** 295 (Sept-Oct) 1928, *Text on Anesthesia*, New Orleans, J A Majors Company, 1926.

We must mention here the fact that the means outlined to prevent explosions from free ethylene in the operating room apply also to gas-oxygen mixtures with ether vapor. Poe¹² stated that mixtures of ether and oxygen are highly explosive, much more so than ether in air. Brown,¹ and Hornor and Gardener² gave figures showing the wide range of ether-oxygen mixtures with and without nitrous oxide which will explode. It is true that ether vapor, being heavier than air, sinks to the floor and to some extent out of harm's way, but that some explosions attributed to ethylene must in reality be blamed on ether cannot be doubted. Guthrie¹³ mentioned "a most unfortunate and widely heralded fatal explosion" which actually occurred while nitrous oxide and ether vapor were being given, although ethylene had been used earlier in the anesthesia.

Our discussion of ethylene explosions up to the present has been limited to those which occur not in the anesthetic apparatus but out in the operating room. Except for the matter of static charges acting as the causative agent in these explosions, it is evident that such accidents are readily preventable by ordinary common sense and a few precautions. Explosions within the machine or accessory parts can be due only to ignition by something inside the apparatus. Static spark is the only agent that can be seriously considered in this connection. Because static charges are responsible for many accidents occurring in the operating room and must be entirely blamed for the explosions occurring within the machine, it is plain that time expended in a careful study of electrostatics and the electrical characteristics of the anesthetic equipment is time well spent.

ELECTROSTATICS AND THE ELECTRON THEORY

It is essential to know at the outset the modern conceptions of the nature of static electricity, how it may be generated and why sparks occur. The electron theory is a simple and adequate means of explaining these phenomena.

According to the electron theory, all matter is made up of atoms, each atom containing a positively charged nucleus about which are grouped in different configurations a varying number of electrons. The arrangement and number of electrons grouped about a nucleus depends on the type of atom with which we are dealing. Thus elements of low atomic weight are made up of atoms having relatively few electrons of simple space arrangement, while for elements of high atomic weight the reverse is true. The electron is conceived to be the smallest

¹² Poe (footnote 11, first reference)

¹³ Guthrie, D. Surg Gynec Obst 43 703 (Nov.) 1926

unit of negative electricity, and since ordinary matter is without electric charge, there must exist in every atom of such matter just enough electrons to neutralize the positively charged nucleus. Suppose that by some means one can rub off or displace from the atoms composing a substance some of the electrons that had hitherto been bound in the atoms. Obviously, if this can occur the positively charged nuclei of the atoms will no longer be neutralized, and the matter will possess what is called a positive charge. Thus it is seen that what is called a positive charge on a body is simply a deficit of electrons or negative electricity. In the same way, a negatively charged body possesses more electrons than are normally attached to it. The familiar experiment of charging an ebonite rod by rubbing it with fur provides an excellent example of this theory. When the ebonite rod is rubbed vigorously with the fur, presumably the friction (energy is required) causes some of the electrons in the atoms of the fur to be dislodged and transferred as free electrons to the ebonite rod. The rod therefore holds an excess of electrons and is negatively charged, while the fur atoms are lacking in some of their electrons and the fur itself is positively charged. From the mechanism involved, it is evident that the amount of negative charge on the ebonite rod must be exactly opposite and equal to the positive charge on the fur. If the charged ebonite and fur are placed in intimate contact for a time, both lose their charges since the free electrons on the ebonite return to their proper places in the fur atoms.

Experience has shown that charges are obtained on rubbing two bodies together only when (1) the substances are of different material, (2) they belong to the class of substances called insulators, and (3) they are dry. Concerning the first prerequisite we can say nothing, except that it is true. Glass cannot be charged by rubbing it with glass, nor does friction of rubber on rubber lead to charge. The second statement needs some explanation.

If one should rub together a bar of iron and a bar of copper held in the two hands, it is possible that charges may be produced on the two metals, but no charge could be demonstrated because these substances conduct electricity, which means that the electrons can move through them without much difficulty. If this is true, any excess of electrons produced by friction on one of the rods can flow around to their original positions through the body of the experimenter. Suppose, however, one rubs a piece of rubber against a steel rod. Friction of the metal on the rubber causes a displacement of free electrons from the steel onto the rubber, so that the latter is negatively charged and the former must possess an equal and opposite positive charge. But

here is a point of great importance. The negative charge on the rubber can be easily demonstrated at the place where the friction occurred but no charge is found on the metal. The answer is very simple, of course, but of great importance in understanding phenomena of exactly the same nature which occur on anesthetic machines. The charge is found on the rubber because an excess of electrons was rubbed off onto it and then these extra electrons could not get away. They stay on the rubber at the point where the transfer occurred because rubber is a nonconductor. It offers great resistance to the passage of electrons through it. No positive charge can be found on the metal rod, because it is a conductor and in direct contact with the body of the observer, which is also a conductor. Assuming the observer to be insulated from the ground, the positive charge will spread uniformly over the entire surface of the observer and rod so the charge at any point is so small as to be impossible of detection.

The reason why insulating substances must be dry in order that static charges may be produced should be evident from the foregoing paragraph. Even a thin film of moisture on the surface of an insulator gives it the characteristics of a conducting body as far as static charges are concerned. Thus static charges by their very nature can exist (be static) only when an insulating barrier is provided. If one touches a highly charged but insulated metal ball with a copper wire leading to the earth the charge on the ball is instantly dissipated. There occurs a transient flow of electrons up or down the wire, as may be necessary for the charged ball to be rendered electrically neutral. This flow of electrons is an electric current.

Static charges, of course, may be generated on an insulated body, or on only a small part of it, by friction with an unlike substance. The size of the charge varies with the amount of energy expended in rubbing the two bodies together, and whether or not the charge remains localized at the site where the friction occurs depends on the insulating properties of the substances involved.

When a body possesses an electrostatic charge, either positive or negative, space surrounding the object is under a state of strain which is called an electrostatic field. This is proved to be true by many phenomena that occur in space near charged objects. Thus mechanical forces of attraction or repulsion are exerted between charged bodies, conductors brought near a highly electrified object become charged themselves. The latter phenomenon is called charge by induction, and it may be of great importance in the present problem. Charge by induction is represented in figure 1.

A metal ball, *A*, is assumed to be strongly charged by a great excess of electrons, $1 e$, it is negatively charged. This charge cannot be lost because the ball is insulated from its surroundings by the glass standard on which it rests. An elongated metal shell, *B*, also supported on a glass rod, is now brought close to *A*. Investigation of the shell with an electroscope shows that its two extremities are highly charged, the side toward *A* possessing a positive, and the opposite end an equal negative charge. If the shell *B* is now withdrawn out of the field produced by *A*, it will be found to possess no charge. In other words, simply by placing this conductor near a charged body, one has produced a transient displacement of the electrons in its substance, a change that immediately disappears when it is drawn out of the electrostatic field. It should be evident that if the shell *B* were made of glass or hard rubber instead of metal, no such changes could occur because in these insulating substances the electrons are not free to move.

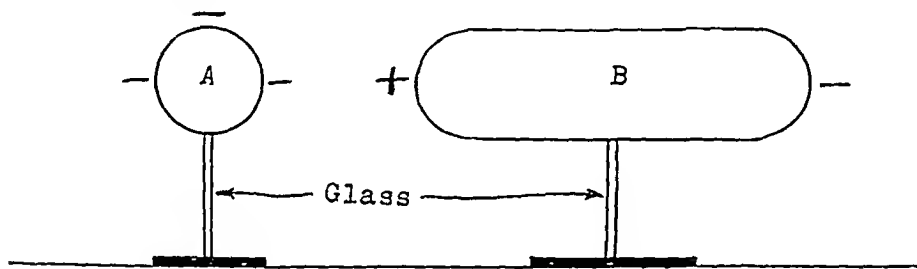


Fig 1—Sketch illustrating electrostatic charge by induction

Suppose now that one continues to bring the metal shell *B* and the charged ball together until only a very short gap lies between them. Charges will be induced on the two ends of *B*, as we have described, and if one possessed means for measuring it, one would find an appreciable force of attraction between *A* and *B*. If one shortens the gap still more and watches closely, a spark will be seen to jump between the two conductors. A static spark has occurred. As the charges are approximated, the electric field between them becomes more intense until finally the insulating power of the air breaks down and a stream of electrons passes over the gap, leading to a more or less perfect equalization of the charge over both conductors. Investigation of *B* after the spark has occurred will show that it now possesses a negative charge spread over its surface.

In the foregoing paragraph we have assumed both the charged ball and the shell to be conductors of electricity. What will occur if one or both of these bodies are insulators? First, let it be assumed that the ball *A* is made of hard rubber and is highly charged as before with a negative charge. As the shell, which is of metal, approaches the ball,

charges will be induced on its extremities as described. Finally, as the interval between the two becomes very short, a spark occurs, but this spark is very small and has little energy behind it. The reason is found in the fact that although the rubber ball possesses on its surface a tremendous excess of electrons which it would like to get rid of, it cannot do this because they are bound by the insulating character of the ball to stay where they are. In other words, the excess charge has only been removed from the ball at the point of nearest approximation with the shell, to equalize the charges, as was accomplished by a single powerful spark from the metal ball, one would have to approximate, or even touch, the shell to the ball many times over a greater part of its surface.

If the charged ball were made of metal and the elongated shell of rubber, no induced charges would be noted as the two are brought together, and should a spark occur between them it would be very weak indeed. Again to equalize the charges on these two bodies one would be forced to touch, or very closely approximate, a great many points on the shell with the charged ball. If both objects are made of insulating material, the charges on the two could be equalized with even greater difficulty, and sparks of appreciable size would be hard to obtain.

All this discussion simmers down to something that all have experienced. As a child, one was accustomed to rub one's feet over the carpet during the cold winter months and then discharge oneself by touching the back of father's neck or some other convenient conductor of electricity. It was soon found out that the biggest spark was obtained by touching a radiator, the best and largest conductor in the room, and that no spark would result if one touched the wall or other insulating material. It was also found that no sparks were produced when persons touched each other, a phenomenon that demonstrates an all-important truth. It is not the magnitude of the charge on two objects that will determine whether or not a spark will occur between them, but it is the difference in electrical potential that is important. Sparks cannot occur between various metal parts on a gas machine if they are connected together electrically, no matter how highly charged the entire mechanism may be.

It has been shown that electrostatic induction plays an important part in the production of static sparks. It is further important in that pieces of metal, simply by being placed in the vicinity of a charged body, become charged themselves by induction and thus become a potential source of static spark. It is conceivable that a highly charged object merely by being adjacent to a gas machine could induce on the

latter charges that might lead to a spark and the ignition of explosive gases

A static spark represents the release of a certain amount of energy that has been stored in the field surrounding a charged body. One sees the spark, one hears it, and, furthermore, energy is liberated in the form of heat which may suffice to ignite anything inflammable nearby. It is important to keep in mind that the static spark is only a means of equalizing differences in electrical potential. It is not unlike the rush of steam from the safety valve on a boiler. When the pressure difference, either steam or electric, exceeds a certain amount, the connecting medium breaks down and a rush of steam or electricity results. The ability of the spark to ignite an explosive mixture will depend on two factors: (1) The amount of energy dissipated in the spark and (2) the readiness with which the mixture explodes. The energy liberated by the spark will be greatest when the charge is very large and when the bodies between which the spark is to occur are conductors, so that all the energy stored up in the electrostatic field can be expended at once. We have shown that the explosibility of mixtures of ethylene and oxygen varies with the concentrations of the two gases present.

Let us now endeavor to apply to the present problem some of the principles that we have just laid down and see if we are not able by such a method to come to some conclusions concerning the rôle that static charges may play in the operating room. In the discussion that follows, much will be said that applies specifically to the McKesson Model G apparatus, and for that reason certain of our conclusions may not be true for machines of different make. The general principles will remain true for machines of all types, but structural variations make a great deal of difference in the theoretical possibilities.

Before entering on the next discussion, a word should be said about the well known fact that static spark occurs particularly in the winter months and, it might be added, in the colder parts of the country. The reason for these facts is, of course, found in the lower humidity in the winter months and in the colder climates.

APPLICATION OF THE ELECTROSTATIC THEORY TO THE ANESTHETIC MACHINE

The McKesson Model G machine is essentially a rugged and under-slung platform made of steel and supported by three rubber tired wheels. The single wheel at the front of the machine is fastened at the lower end of the metal post on the top of which are located the mixing chamber, automatic shut-off valves and the mechanism that

supports the supply bags, one on each side of the metal post. To the front side of the mixing chamber, the ether chamber and the rebreather, all in one unit, are securely held by a metal coupling. At the opposite extremity of this device is the metal connection over which the hose leading to the patient is slipped. The gas tanks rest, of course, on the low platform and are supported by a chain attached to a stout metal

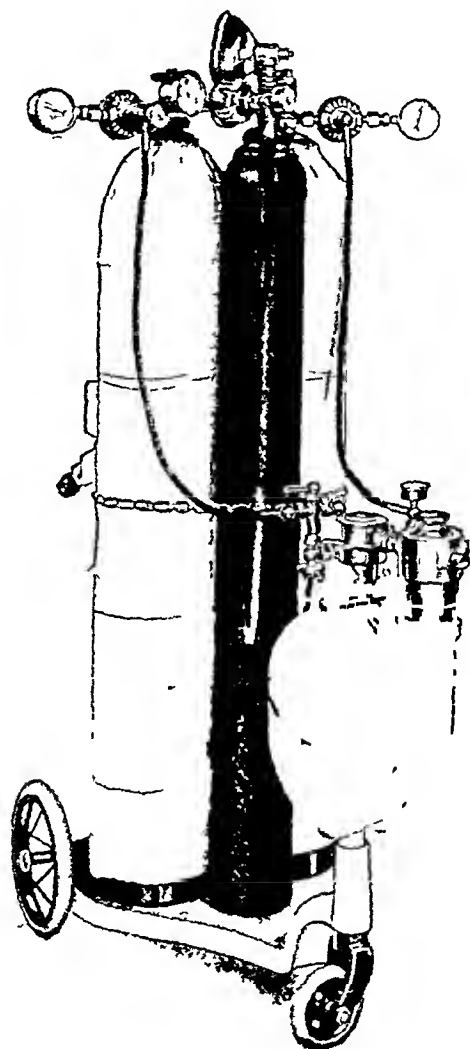


Fig 2—McKesson model G anesthetic machine (Cut supplied through the courtesy of Dr E I McKesson)

post arising from the back of the machine. The cut from the instruction book of the McKesson people should make the layout of the machine reasonably clear.

The important points about the construction of the apparatus are 1 There is sure metallic connection between all parts of the metal carriage and the important parts mounted on the head of the machine clear out to the outlet to which the hose attaches. 2 The tanks are

grounded to the carriage by means of supporting chains attached to the posterior post. It should be noted that the insulating cloth tank covers shown in figure 3 are not used in this hospital. To be doubly sure that the tanks are electrically connected to the frame of the machine, the rubber mat on which the tanks rest should be removed or holes pierced in it so that the tanks may stand on the frame itself from which insulating paint has been removed. 3 The entire apparatus is insulated from the floor by means of the rubber tires with which the machine is provided. 4 The breathing tubes are made of rubber in which is embedded a spiral conductor running the full length of the hose and making electrical connection with the metal collars at both ends. If a metal facepiece is employed, there exists an uninterrupted metal circuit from the metal rims of the wheels out to the facepiece. This means that if a charge is imparted to any metal part of the apparatus, all the metal on the machine receives equally the charge, and no sparks between metal parts can occur. It also means that the gas machine constitutes a conductor of considerable size so that, as observed in our theoretical discussion, the stage is set for a lusty spark should a charged body be brought near.

It should be pointed out that simply grounding a machine, as we have described, is worse than not grounding it at all if, at the same time, precautions are not taken to prevent charges from being brought near the apparatus. The effect of grounding the machine is to cause it to act like a conductor of infinite size, thereby making possible a static spark of maximum size. This matter is of extreme importance, as we find many users of gas apparatus grounding their machines in the belief that they have found the panacea that eliminates the danger of static discharges. Even at the risk of repetition, let us be sure that what is accomplished and what is not accomplished by simply grounding a gas machine is understood.

The usual practice is to run a copper wire from some point of the machine to a water pipe in the operating room. This accomplishes one thing. As long as the ground connection is intact, it maintains all the metal parts on the machine at the same potential as the ground, i. e., a zero potential. For this reason, no charges can be built up on the metal parts of the machine by passage of gases through certain parts of it or by other means acting within the apparatus. To this extent, grounding a machine may be desirable, but, as will be shown later, the production of charges on the metal parts of the machine by causes acting within the apparatus are of minor importance. Suppose a nurse comes rushing into the operating room carrying a high static charge with her. The grounded gas apparatus offers the best means for her

to get rid of the charge most rapidly and completely (like the radiator of our childhood days), so she proceeds to touch some part of the anesthetic equipment (or the table or patient, perhaps also grounded). Unfortunately the spark jumps quicker than her finger can move and before she touches any metal part, the spark has occurred, and perhaps an accident. Obviously, grounding of the anesthetic equipment, table and patient is worse than useless in preventing sparks due to charges that are generated outside and are brought into the danger zone. We will describe later the methods that have been used to eliminate these exogenous charges in other institutions.

STATIC CHARGES PRODUCED BY MOVEMENT OF THE GAS MACHINE

We will now describe the different parts of the apparatus and the things occurring in the operation that might conceivably lead to the production of charges on the gas machine.

Movement of the entire apparatus from the anesthetic room into the operating room or along the corridor facing the operating rooms may lead to the production of charges on the rubber tires of the machine. Equal and opposite charges are, of course, left on the floor over which the machine passes. This could not occur on floors that are damp or that are composed of a substance like the tires (i. e., made of rubber), but on dry linoleum, wood or tile floors charges are extremely likely to occur. The amount or the intensity of the charge that can collect on the tires will depend on the amount of actual friction that occurs between the tires and the floor and the excellence of the insulating qualities of the rubber in the tires. Obviously, sliding a machine sideways will lead to greater charges than simply rolling the machine, and damp weather or water on the floor will entirely prevent the accumulation of charges on the tires. It should be understood that charges produced by movements of the machine generate charges only at the points of contact of the tires with the floor, that is, at the periphery of the tires. If the charges remain in these locations they are of less importance than if they spread over the machine, although it must be remembered that even an extremely high charge on the tires would, when distributed over the entire metal parts of the machine, be greatly decreased in intensity. If the tires are excellent insulators—which is another way of saying if they are dry—the charges will be confined to the tread of the tires. If some leakage can occur, part of the charge will be lost on the floor and part will leak onto the machine.

A way in which static charges existing at the periphery of the tires may be of importance is by producing induced charges on the interconnected metallic elements of the machine. As we have described, a

negative charge existing on the tires would cause a positive charge to be induced at the nearest point of the conductor, which is here the metal rims of the wheels, and an equal negative charge to appear at the opposite end of the conductor, which would, of course be at the tops of the tanks and on the metal facepiece. A person or conductor touching these points might cause a spark to occur. However, it must be remembered that the area over which these induced charges would exist is a large one and that an extremely intense charge on the tires would be required to induce negative charges of consequence on the tanks or the facepiece.

Herb,³ and Allen and Murray¹⁴ have reported explosions that have occurred while the gas machine was being moved from the anesthetic room. Nitrous oxide-oxygen and ether were in use when the accident took place in Chicago, whereas ethylene was being used in Detroit. In each of these instances it is difficult to attribute the trouble to charges that had accumulated by movement of the machine. Too many exogenous sources of static are present, the importance of which are definitely established.

Although it seems that explosion from charges generated by movement of the anesthetic apparatus can be regarded as unlikely, such a source of danger must be kept in mind. On several occasions when a gold leaf electroscope was used we found appreciable charges on the tires of machines that had just been wheeled from the anesthetic rooms across the hall into an operating room. It was also found that these charges immediately vanished when the machine passed over a portion of the floor that had been recently mopped. In eliminating danger from this source, then, one must remember that a little moisture will prevent charges from being generated or from remaining on the tires. Particular attention should be paid to this matter in dry cold weather when the machine has to be transported for some distance.

STATIC CHARGES PRODUCED BY MOVEMENT OF ANESTHETIC GASES IN THE MACHINE

We will now discuss the problem of charges that are produced on the machine itself when the apparatus is in operation. We have said that charges are produced only when a certain amount of energy is expended as friction between unlike substances. One is forced to conclude that the possibilities for generation of static are decidedly limited. The only conceivable sources of charge on or within the apparatus are due to the passage of gases through the system or to movement of certain parts of the machine directly caused by the gaseous movement. It is plain that in only two places on the machine can such movement occur

14 Allen, C. I., and Murray, M. *Surg Gynec Obst* 44:690 (May) 1927

They are, of course, the rubber supply bags (with the automatic shut-off valve mechanism) and the rebreathing bag, provided that rebreathing is being employed. We will first discuss the possibility of charges being generated by movement of the anesthetic gases themselves.

Luckhardt¹⁵ pointed out the ability of gaseous mixtures flowing through an insulating tube to produce gradually static charges thereon. It is also known that liquids (not aqueous) flowing through nozzles or constricted orifices may lead to the generation of dangerous collections of static electricity on the nozzle or in an insulated tank into which the fluid falls. Gasoline has been exploded by charges originating in this way.¹⁶ Furthermore, jets of steam passing out through small orifices from high pressure boilers or steam lines may carry a high charge. This steam striking a conducting object may impart the charge to it, so that many strange and perhaps dangerous phenomena may be directly traceable to an innocent appearing steam jet. It is interesting in this connection to recall that some of the early machines for the generation of large static charges used the principle of multiple jets of steam striking on an insulated conductor from which large charges could be obtained.

There exist two places on the gas machine where one might expect sizable charges to be generated by gaseous friction. The first location is at the reducing valve attached to the top of the gas tanks and the second is at the automatic shut-off valves located on the head of the machine. The reducing valve operates under a great pressure, 1,000 pounds (453.6 Kg) per square inch, or more, on one side, and a much lower pressure, from 40 to 60 pounds (18 to 27 Kg) per square inch, on the other side. Obviously the pressure gradient within the valve is tremendous, and within the highly constricted space through which the gas must pass, its velocity must be very great. One often has evidence of the great amount of decompression which occurs within the valve in frost which collects outside it. Why then does one not find large charges produced at this point? The answer to this question must be found in the construction of the valve and its housing. If a jet of gas were released to the outside from an ethylene tank, for example, with no intermediate valve, it might well be highly charged and impart its charge to any conductor on which it impinged. However, the expansion of the gas occurs within a closed chamber that is made entirely of metal. Therefore, even if charges are produced at the point in the valve where the gases undergo decompression, the charges tend to

15 Luckhardt, A. B. Potential Dangers Attendant on Ethylene-Oxygen Anesthesia, *J. A. M. A.* 82:1603 (May 17) 1924.

16 Standard Handbook for Electrical Engineers, ed. 5, New York, McGraw-Hill Book Company, 1922, p. 1850.

be lost immediately because the charged particles of gas are attracted to the metal wall of the valve where any electrons that might have been displaced by the friction incident to the decompression process are free to return to the molecules from which they were removed. The whole point of the matter is this. Friction between gas and metal of valve may lead to charges on both. These charges must be opposite and equal, and following decompression, opportunity for neutralization of the charges is provided especially because the charged atoms of the gas are attracted to the oppositely charged metal. Let us emphasize here that should a charge be generated at the reducing valve it would appear diffusely spread over the metal parts of the machine, for we have shown that all these parts are electrically connected.

What has been said concerning generation of charges at the reducing valve applies equally to the automatic shut-off valves. It is clear, then, that if our ideas are correct, little danger from generation of charges by the gases passing through the metal parts of the machine can be anticipated. Tests with the electroscope on a considerable number of machines in operation have failed to reveal the slightest charge on the metal parts of the apparatus. It should be pointed out, however, that in operation the anesthetist is connected to the metal of the machine by her fingers on the facepiece and that the patient is also in the circuit as a result of the same contact. The anesthetist by her contact with the floor or the patient through the table may provide a path of leakage for charges originating on the machine. However this may be, it is evident that even under the system of operation in many hospitals, one involving no precautions for the elimination of sparks, charges on the metal of the machine are either not produced or are satisfactorily taken care of. Grounding the machine to a metal floor will absolutely eliminate danger from charges arising on the metal parts of the equipment.

Gases from the tanks pass down to the head of the machine through rubber tubes, then from the automatic valves into the large supply bags, from which they pass to the mixing chamber. From the mixing chamber the gaseous mixture, which may now be explosive, either passes directly out through the ether attachment and rubber hose to the patient or may be shunted through the rebreather before entering the hose. As we have pointed out, sparks occurring inside the machine cannot lead to explosion at points in the apparatus before mixture of the anesthetic gas with oxygen occurs. Thus explosion in the tubes leading from the tanks to the supply bags or in the bags themselves cannot take place, providing the machine is operating properly. This provision is added because it is possible, should the check valve at the bottom of the mixing chamber fail to seat perfectly, for contamination of gas in one supply bag from gas in the other to occur.

If by this means ethylene should leak into the oxygen bag the resulting mixture might be highly explosive. It should be stated here that the probability of the check valve not properly seating is not great, particularly if it is occasionally removed and inspected to see that it is clean and dry.

We must now conclude our discussion of charges that may arise by passage of the gases through the machine by considering the situation presented in the nonconducting portions of the apparatus.

We cannot say definitely that charges are not produced by passage of the gases through the rubber hoses employed. If any do exist they are located on the inside superficial portions of the rubber, and as the tubes are of uniform bore, one would expect the charge to be uniformly distributed along its walls. This being true, sparks could not occur between adjacent portions of the inner surface and, furthermore, electrified atoms of gas would be attracted to the charged rubber located more distally, so that conditions for neutralization of the charges, to a certain extent at least, would be provided. It should also be remembered that the velocity of the gases, particularly in the large breathing hose, is not extremely great, and one finds difficulty in understanding how friction sufficient to produce appreciable charge can result.

If the small hoses connecting the tanks with the supply bags receive a charge, it must be insignificant, since a number of tests with the electroscope have failed to reveal any static on these parts. The same is true of the larger breathing hose. Static charges occurring in the small hoses are of no importance as far as the danger of explosion in them is concerned, for obvious reasons. The opposite state of affairs prevails with regard to the breathing tube, so that precautions must be taken to prevent charges therein, no matter how vague the possibility for the existence of such charges may seem to be.

To be certain that the charges do not collect within the breathing hose, the entire inside of the hose must be made of conducting material electrically connected at the two ends to the metal collars one of which slips over the attachment on the ether chamber and the other onto the metal facepiece. The tubes that are supplied with the McKesson machine are constructed with a closely wound spiral conductor embedded in the rubber on the inside of the tube. If this conductor is in actual contact with the gases throughout the inner surface of the hose and makes satisfactory electrical contact with the metal end-pieces, the tube is safe as far as charges generated by passage of gases within is concerned. It should be pointed out that a spiral conductor deeply embedded in the substance of the rubber hose and not projecting into the lumen of the tube is powerless to prevent accumulation of charges on the inner rubber surface. It is not only useless in preventing inside charges, but it may provide a source of static spark since, as has been shown, a conductor

in close proximity to a charged body has charges induced on it and the insulating medium between them may rupture leading to a spark

We have shown that the passage of the gases themselves through various parts of the machine is certainly not important as a source of charge within the machine. Explosive mixtures exist only in the mixing chamber and from there outward. Sparks cannot occur in the mixing chamber because it is entirely of metal interconnected with the rest of the machine. The same argument applies to the ether attachment and the rebreather (with an important exception to be considered later). The hose, however, may contain an explosive gaseous mixture and at the same time present the fuse necessary to set the mixture off. It is important to be sure that the hose is designed so that charges cannot collect within its lumen.

CHARGES PRODUCED BY MOVEMENTS OF RUBBER REBREATHING OR SUPPLY BAGS

Gases passing through the anesthetic equipment can cause charges to arise not only because of friction of the gases themselves on certain parts but also indirectly by causing motion and hence friction between adjacent structures. The supply bags are periodically distended and deflated during the operation of the apparatus, and friction occurs between the rubber bag and the coarse mesh that surrounds it and between the bag and the metal arm attached to the mechanism of the shut-off valve. When rebreathing is employed, the rubber rebreathing bag expands and contracts in synchronism with the patient's respiration, so that friction occurs between the rubber bag and the bottom of the metal chamber. The problem presented by the rebreather will be considered first.

The rebreathing chamber is a cylindrical metal shell about 8 inches (20.3 cm) long terminating in a rounded bottom in which several good-sized holes are punched. The upper end of the chamber is screwed into the under surface of the ether attachment. To vary the amount of rebreathing and to make the system a closed one, a cylindrical rubber bag, fastened on a movable metal ring encircling the metal shell, is fitted over the bottom of the device. A fine mesh net cover is provided for the rubber bag. As these bags are made of thin rubber they deteriorate after some time and have to be replaced. As a matter of convenience in this hospital, as the original bags with the net wore out, rubber gloves were substituted for them. Thus practically all the machines now in use have been equipped with a bare rubber glove which serves as the extremity of the rebreathing space.

As McKesson¹⁷ pointed out, respiratory gases never reach this end of the rebreathing system since its capacity is far too great. For this

17 McKesson. Instruction Book for Model G Apparatus

reason, the rubber glove is always perfectly dry and contains only mixtures of the anesthetic gases and ether vapor, if the latter is being used. It is hardly necessary to say that at some time during ethylene anesthesia, highly explosive mixtures of gases may exist here and, furthermore, that with the administration of nitrous oxide-oxygen and ether vapor the same may be true.

Observation of the rubber glove when rebreathing is being used proves that a certain amount of friction between the rubber and the rebreather is always present. During expiration the glove is ballooned out so that it makes scanty contact with the metal shell but during inspiration the rubber is drawn tightly against the sides of the chamber and the fingers of the glove against the rounded bottom. The amount of friction at this point varies with the depth of the patient's respiration and the amount of rebreathing employed. Theoretically, in this arrangement the stage is set for the generation of charges. By actual tests with the electroscope, charges, often of great intensity, are regularly found on this rubber glove, especially toward its lower part. As a matter of fact, this glove was the only place on the machine where, during its operation, charges could be demonstrated.

It is a matter of great interest to us to find how well the actual electrostatic observations on the machine coincided with the theoretical possibilities. For example, friction of rubber on metal is supposed to result in a negative charge on the former and a positive charge on the latter. The electroscope proved the charge on the glove to be, in fact, negative. A positive charge of equal magnitude must, of necessity, be generated on the metal rebreathing cylinder, but since the rebreather is only a small part of the interconnected metal parts of the machine over which this charge must be distributed, no positive charge can be demonstrated. Moreover, another important fact must be remembered. Contact between the metal anywhere on the apparatus and a person or other conductor will further distribute the positive charge. As a matter of fact, during an operation the anesthetist and patient are grounded to the metallic elements of the apparatus, thus receiving their shares of the charge and offering further paths for its dissemination. Conditions on the rebreathing glove are much different. Because of the insulating nature of the rubber, the negative charge on the glove cannot be conducted away. The entire charge is bound to remain in situ, and its intensity is correspondingly great. Thus, by actual test, high negative charges are found on the rebreathing glove and nothing on the metal of the machine, although equal positive charges must have existed thereon, momentarily at least.

Tests of the magnitude of the charges produced on the rubber glove by means of an electroscope giving quantitative readings have shown

that potentials of several hundred volts are common. The length of time over which charges may persist on these gloves is considerable. Four machines in the anesthetic work-room were examined for charges at 2 p. m. None of these machines had been used since noon and some had been idle for three hours. High charges were found on the rubber glove on three of the four. The one machine on which no charge was present was equipped with the original McKesson rebreathing bag with the net covering.

The presence of a mesh cover over the rebreathing bag has been thought by some to be a source of danger by virtue of friction between the two leading to static charge. Our experience does not seem to confirm this belief. In fact, the one machine equipped with the original bag and net is the only one on which charges have not been found during the course of an anesthesia. To explain this, it seems that one must assume that friction of cloth against rubber is not so potent a source of charge as friction of rubber against metal. Of the latter, there can be no doubt.

An extremely important point in connection with a charge arising on the rebreathing bag is its location. Is the charge inside or outside of the bag? Obviously, charges produced on the inner rubber surface and leading to spark within the bag are much more serious than external charges and sparks on the outside. It should be plain that friction of a rubber bag with a net cover can result only in charges accumulating on the outside of the bag, for this reason, even should charges between the netting and the bag be evident, we cannot consider their presence to be extremely dangerous.

In view of the foregoing discussion, it can be seen that the charges generated by friction of the rubber glove on the metal rebreather are highly dangerous. The charge on the glove is on its inner surface, and as parts of the rubber are continually being drawn in close proximity to the metal shell, sparks are likely to occur between the two. If the mixture in the rebreather happens to be an explosive one at the time the spark occurs and the spark liberates sufficient heat to ignite it, a tragedy is inevitable. Many facts lead us to believe that such a mechanism was responsible for a fatal explosion which occurred in the maternity wards of the University Hospital several years ago.

It is evident that the rebreathing bag, as it is being used in this hospital at the present time, constitutes a real point of danger. The fact that ethylene is not being employed does not eliminate the hazard, for ether vapor and oxygen may, in proper proportions form highly explosive mixtures. This is a serious defect in the use of the machines which must be corrected even though the further use of ethylene is not contemplated.

The obvious method of preventing accumulation of charge on the rebreathing bags is to so modify them as to make them conductors of electricity. If, by some method of manufacture or some type of treatment, the rubber could be changed from an insulator into a conductor the problem would be solved. Some work has been done along these lines in the preparation of a leaded rubber bag. For some reason, however, this product has not appeared on the market. The use of water in the bags does a great deal to eliminate charges which might otherwise collect on the glove. The routine use of this method for prevention of charges is open, however, to two objections. 1 It does not seem to do the job. It must be remembered that the gaseous current through the rebreather may be very rapid and that water placed in the glove evaporates rapidly. It has been found that when the water becomes low in the fingers of the glove, upper portions of the rubber may be dry and possess slight charge. 2 It does not seem wise, at this important point, to rely for protection on a bit of routine which, after months of uneventful operation, may slip and result in a dry glove at the time when protection is most needed. Even with a staff of highly trained anesthesiologists, such as we possess in this hospital, it seems unwise to have the safety of the patient depend on the personal factor. Particularly is this true if other better means can be devised.

Prof. N. H. Williams, of the Physics Department of the University of Michigan, has suggested the use of a manometer or U-tube containing fluid to replace the rubber bag. In order that such a device may be used to measure the tidal air, as is done when the bag is employed, the layout shown in figure 3 should prove satisfactory.

As can be seen by inspection of the drawing, the rubber bag is replaced by a U-tube made of sheet metal. The proximal arm of the tube is securely soldered to the metal ring which slides over the rebreathing chamber. A liquid—water, glycerin or mercury, depending on the terminal resistance desired—is placed in the U-tube. Obviously, air forced into the rebreather under pressure will raise the liquid in the distal arm until a pressure balance is secured.

To measure the tidal air with the manometer device, one must first slide the U-tube up as high as it will go by moving the ring attached to the proximal arm up the rebreather. The fluid level in the manometer is then adjusted so that it lies just at the convex bottom of the rebreathing chamber. The tidal air is found by sliding the U-tube down until the correct volume is obtained, using the calibration on the rebreather. When the correct point is reached, that is, when the volume of expired air just fills the space between the bottom of the rebreather and the fluid level, the liquid in the manometer, as seen through the glass window, will oscillate perceptibly at each respiration. During this process the

expiratory valve on the facepiece must be adjusted so that no air escapes from it. This device may be open to criticism on the ground that it is rather bulky and cumbersome. On the other hand, it would eliminate the danger so inherent in the use of a rubber bag. Moreover it must be remembered that the manometric device need never be replaced and requires nothing but an occasional readjustment of the fluid level.

A means for avoiding charges on the rebreather which may prove to be valuable is the use of a radioactive substance in the bag. It is well known that radioactive substances, by the emission of alpha, beta or gamma rays, cause ionization of the surrounding air so that the air itself may become a conductor of electricity. The rebreathing bag is not large and it seems that the use of some ionizing material within it

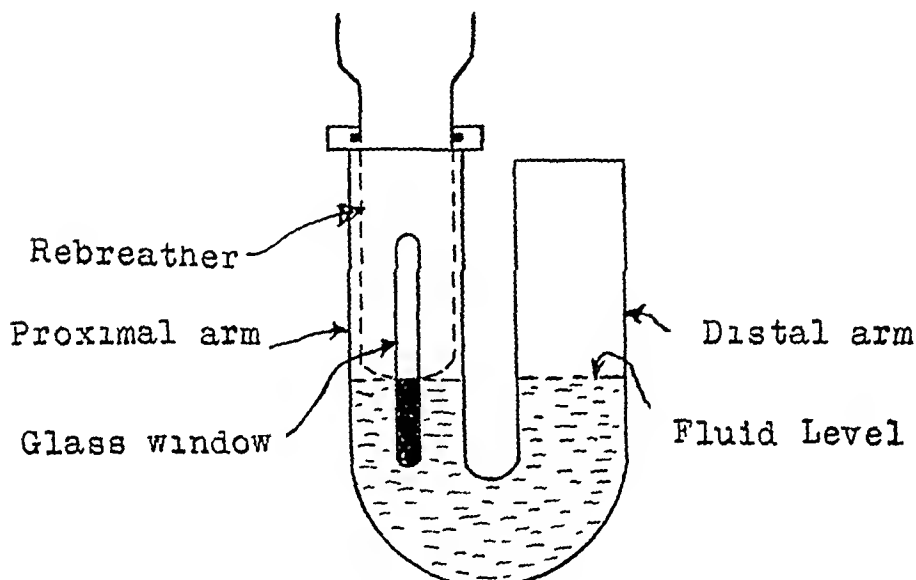


Fig 3—Manometric device to replace rubber rebreathing bag

might so alter the character of the air within and around the rubber as to prevent the accumulation of charges thereon. Because of its simplicity, a trial of this method would seem to be advisable.

A considerable amount of space has been devoted to the discussion of charges on the rebreather because it is felt that, under the present operating conditions, danger is always present at this point. It should be strongly emphasized that an explosion in the rebreather is very likely to be fatal to the patient because the explosion travels in both directions from the point of ignition, back into the mixing chamber and out through the hose, even into the patient's air passages. Explosions occurring outside the machine are not so serious because the explosion is not confined to a closed space in direct communication with a person's vital organs.

Little has been said up to the present concerning charges existing on the large rubber supply bags. The danger of explosion within these

structures, except under very unlikely circumstances, as we have shown, is nil because they contain pure gases from the tanks. Charges existing within the bags can occur only by friction with the gases in them, since there is no source of metallic friction. This condition may arise but it is difficult to understand how charges so produced can be of any importance. Charges on the outside of the supply bags may arise either by friction between the rubber and the enclosing mesh or by friction between the metal arm, attached to the automatic shut-off valve, and the bag. Neither of these sources of static can be very important because, during the operation of the machines no charges have been found on the bags, with the electroscope. To be sure that charges do not collect on the bag it should be made of conducting material. Perhaps the use of a radioactive substance in or on the bag, should such a method prove valuable on the rebreather, would be advisable as a safety-first measure. At the present time, it seems that one can regard static charges on the supply bags as of minor importance, although it would be advisable during the cold winter months to test these parts occasionally with an electroscope to be sure that our view is not in error.

In our discussion we have covered charges that arise on the machine, either by its movement or through its actual use, and means whereby they can be prevented. We have yet to consider methods of preventing static charge outside of the machine.

STATIC CHARGES ARISING OUTSIDE OF THE MACHINE AND THEIR PREVENTION

It is evident from the foregoing discussion that during the operation of the McKesson machine there exist very few places on it where charges may be generated or accumulate thereafter. Charges produced by forces operating outside of the anesthetic equipment are harder to classify. It is evident that they can be brought into the operating room by persons or objects entering it, or charges can be produced inside the room by movement of persons or friction between bodies therein. A system for prevention of charges within the danger zone must (1) maintain the anesthetic equipment, patient, table and surrounding objects at the same electrical potential from the time the anesthesia is started until it is finished, (2) prevent persons or objects from approaching the operating table or entering the room while carrying charges, (3) include a realization of the fact that charges can be generated and can collect on insulating bodies near the patient if care is not exercised to prevent friction between such objects. For example, the patient's hair might be brushed by some unintentional movement and a charge thereby be generated.

To maintain the machine, patient, table, etc., at a constant potential, a floor of conducting material to which these objects are electrically joined, either by chains hanging from metal parts or by direct contact, must be provided. The installation at the Presbyterian Hospital in Chicago accomplishes this by a carefully designed floor which has been described by Herb³. Their problem was not extremely difficult because the anesthetic rooms in the Presbyterian Hospital are not separated from the operating rooms by a corridor as they are in the University Hospital. To take care of the situation here, metal sheeting, either of rustless steel or copper, should be placed on the floor of the anesthetic rooms. Directly continuous with this and extending across the hall and into the operating room should be laid more sheet metal of sufficient width to make sure that the machine remains on the metal on its passage to the operating room. Inside the operating room there should be laid a large sheet of the same material, of sufficient size to accommodate the entire surgical ensemble, with a liberal margin around the edges. This sheet should, of course, be directly connected with the one entering the operating room from the hall. It should be noted that the thickness or amount of metal in these sheets has nothing to do with their electrical efficiency. The sheets could be made of gold leaf and still serve satisfactorily as a conducting medium if they were mechanically able to stand the strain. In other words, the metal sheeting which is used need only be thick enough to possess satisfactory mechanical wearing qualities.

The machines should be equipped with metal chains fastened electrically to the frame of the machine and dragging an inch or so along the floor. Any other tables or stands used near the operating table should be similarly provided with chains so that all metal objects in the proximity of the table are kept at the same potential as the rest.

Nothing specific has been said about grounding the metal sheets which are to be laid on the floors. It should be evident that if all the sheets are properly joined and the chains are properly connected to the moveable equipment and make contact with the floor, all the metal parts must be at the same potential and sparks between metallic elements of the system are therefore impossible. This is true whether the floor is grounded or not. The only advantage that can be secured by grounding the system is the assurance that the whole outfit will always remain at the same potential, i. e., a zero potential. It is conceivable, but unlikely, that all the interconnected metal parts might achieve an appreciable positive or negative charge so that spark might occur on contact with a neutral body. We have shown that a large conducting system, particularly a grounded one, offers the best opportunity for sparks of maximal size when a charged body is brought near. This hardly con-

stitutes a sufficient reason for not grounding the floor, but a grounded metal floor presents some danger of short circuit or electric shock since one side of the electric power supply to the hospital is also grounded and the floor may thus act as one terminal of an electric circuit. Difficulty in this direction is especially apt to be found when electrical devices are used in the operating room. In view of the evidence, it would seem advisable to leave the interconnected metal floor ungrounded, at least until some evidence is forthcoming to show such a course unwise. It should be pointed out that grounding can be done easily at any time if it is thought advisable.

In an effort to prevent the entrance of any one to the operating room who might carry a charge, a strip of sheet metal should be carried up on the outside of the doors leading to it. These metal pieces must be electrically connected to the sheet metal flooring and so placed on the door that one must touch them when pushing the door open.

No matter how complete and thorough the means for interconnecting the metallic parts of the operating room equipment are, it must be remembered that charges may still be generated and exist on insulated portions of the apparatus or of other objects within the danger zone. Friction between nonconducting substances, particularly rubber and other materials, must be avoided. The practice of hastily stripping the cotton sheets off the protecting rubber one immediately following the removal of the patient from the operating table will invariably produce high charges on these sheets in suitable weather. The possibility of explosive mixtures of anesthetic gases existing at this time is, of course, not great but one cannot blindly rely on their absence. We have shown that friction of dry rubber on metal is a potent source of static charge. Rapid transfer of metal surgical instruments by persons wearing rubber gloves might lead to production of charges and to serious consequences, particularly at a time when the surgeon's gloves were dry and he was operating on the face or neck.

Friction against the rubber breathing tube might cause the production of charges on its outer surface. For this reason it is advisable to protect the rubber from trauma by winding its outer surface with a coarse mesh of copper wire, securely soldered at the ends of the tube to the metal terminals.

It should be emphasized that sparks occurring outside of the machine are important only because it is possible that explosive mixtures of the gases may be present at the point where the sparks occur. By using a metal floor continuous from the place where the anesthetic is started to the large conductor in the operating room to which the machine and other movable objects are electrically connected by dependent chains, and by using metal plates on all the operating doors so that a person

cannot enter without losing any charge that he might possess, a system is formed that largely eliminates the danger of exogenous charges. As we have shown, however, there exist other sources of static charge which, although they may seem unimportant, must be thought of. Many of these factors are not readily amenable to preventive treatment. In view of these conditions, it seems wise to recommend the use of an additional safeguard, namely, a device similar to the one used by Salzer⁹ which will provide an exhaust pipe for the exhaled gases and prevent their accumulation in the operating room.

As we have mentioned, Salzer employs a metal sleeve which fits snugly over the expiratory valve of the McKesson facepiece. To the sleeve is attached a noncollapsible rubber tube which conveys the expired gases to the outside. Obviously, the rubber tube used for this purpose must be protected, as is the breathing hose, against static charges. A

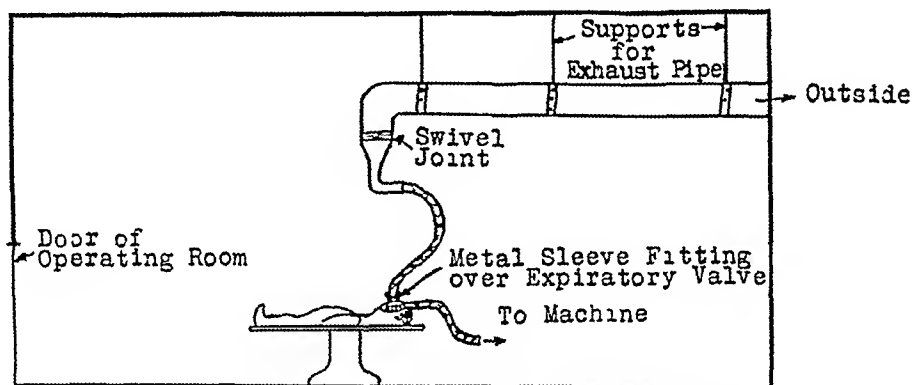


Fig. 4—Arrangement, as suggested by Salzer, for removing expired gases from operating room

piece of the breathing hose covered on the outside by a protective wire network would serve admirably for this purpose (fig. 4).

Before we conclude this section of the paper with a summary of the recommendations for the prevention of anesthetic gas explosions in this hospital, we should briefly consider some of the systems that are advocated by workers elsewhere.

We had the privilege of inspecting the installation which has been employed so successfully at the Presbyterian Hospital in Chicago. We were fortunate in being able to talk with Dr. Herb and with Mr. F. B. Johnson of the Commonwealth Edison Company who was in charge of the investigation carried out in the hospital, which led to the system now in use. The problem at the Presbyterian Hospital was limited to a method that would eliminate static charges arising outside of the anesthetic equipment. The McKesson machine is employed, but since rebreathing is not used, with ethylene at least, charges generated within

the machine were not considered of importance. It is unnecessary for us to describe the details of the system in Chicago for Dr. Herb has done that.³ The installation provides a floor of conducting material, so that chains hanging from the machine and other movable objects can maintain all the metal parts of the equipment at the same electrical potential. The breathing hose is covered by a coarse network of wire, the patient is grounded to the table by an adequate conductor, and attempts to ground the outside of the rubber supply bags and the rebreathing bag to the frame of the machine by means of chains complete the salient points of the installation. An important feature of the floor is that conducting material exists from the point where the anesthetic is started clear through into the operating room and for a large distance around the table so that persons or objects brought near it may lose any charge they may carry before they arrive within the danger zone. It will be noted that this system is essentially the same as the one advised for this hospital, except that it is recognized that a thin sheet metal floor, which is as efficient electrically, will provide a cheap and satisfactory means to the same end, and that the floor which we recommended will not necessarily be grounded, as we believe such a course to have decided disadvantages. It should be mentioned that the system installed at the Presbyterian Hospital has proved its worth. During the four winters in which it has been in use, no explosions have occurred and tests have shown that charges were no longer present in the operating room.

The Gatch method of complete rebreathing employed by Poe¹³ offers definite advantages, as much of the complexity of the anesthetic apparatus is done away with. The places where charges may be produced or accumulate are greatly reduced in number. Moreover, with this method the amount of gas escaping into the room is considerably reduced, so that explosions outside of the anesthetic apparatus are less likely. There are several reasons, however, why the adoption of such a system in this hospital does not seem feasible. 1. The method of administration is entirely different from the one now in use, its adoption would necessitate the purchase of new equipment and the disposal of a large amount of valuable apparatus—a somewhat expensive process. 2. We are forced to wonder whether the method is really as safe as figures would lead us to believe. Has not the freedom from accidents experienced by Dr. Poe and others been partly, at least, due to the more favorable climate in which they live? The use of a rubber bag of some size into which the gases are run and into which the patient breathes does not seem entirely to guarantee the user against explosion which, if it did occur, would be most serious to the patient. The presence of respiratory moisture and carbon dioxide in the bag

can hardly be relied on to prevent the existence of explosive mixtures therein nor can it be said that it is impossible for charges to be generated inside the bag

Lewis and Boehm¹⁸ described a method for preventing static spark on or near the machine by a method of combined metallic interconnection and grounding of the apparatus by means of wet towels, placed on the operating floor. The method seems to have settled the problem in their institution, but certain phases of the system seem rather inadequate to provide complete protection under all circumstances. In the first place, the simplicity of the method depends on the assumption that floors are grounded conductors. The tile floors ordinarily found in operating rooms may not be perfect insulators but they cannot be considered as good conductors of electricity. One must remember that the tiles are made of vitreous clay and are not unlike the material used for insulators on high tension transmission lines. It seems unlikely that, unless it is wet, the floor in their own hospital is able to conduct electricity and, hence, that it is grounded at all. In the second place, the use of moist cloths to transfer charges from the machine or patient to the floor is open to the objection that this means of protection introduces the "personal factor" into the situation. Through carelessness the cloths may not be moistened all over and the question is always to be asked, are the cloths still wet?

SUMMARY OF RECOMMENDATIONS FOR PREVENTION OF EXPLOSIONS

We believe that the following recommendations will provide a safe and workable system for the prevention of explosions during the use of ethylene oxygen or other anesthetic mixtures in this hospital

General Measures—1 Enforcement of strict regulations prohibiting the use of electrical equipment or any obvious source of heat in the vicinity of the anesthetic equipment

2 The suggestions of Dr McKesson for the technic of ethylene administration should, in general, be adhered to

Measures to Prevent Explosions due to Static Spark Outside of the Machine—1 Thin sheet metal (either copper, brass, or rustless steel) flooring forming a continuous pathway from the anesthetic rooms across the hall into the operating rooms where it should cover most of the floor space

2 Chains electrically connected to and suspended from the anesthetic machines and other movable equipment so as to drag on the metal floor

¹⁸ Lewis, W. B., and Boehm, E. F. A Simple Method of Eliminating Danger of Explosion Due to Static Spark in Gas-Oxygen Apparatus, J. A. M. A. 84 1417 (May 9) 1925

3 Inspection of breathing tubes to be sure that the spiral conductor embedded therein projects into the lumen of the tube and that it is electrically joined to the metal pieces at the extremities of the hose. The breathing tubes should be covered by a coarse network of copper wire which should likewise be soldered to its metal ends.

Metal plates, connected electrically to the metal floor, should be placed on the outside of all doors leading into the operating rooms in such a way that one cannot open the door without touching the metal plate.

4 Connection between the patient and the metal frame of the operating table by means of a chain ending in a suitable piece of metal which must rest against his skin.

5 Holes cut in the rubber mat on the carriage of the machines and insulating paint removed from the metal platform at these points so that the tanks will be positively grounded to the frame of the apparatus.

6 A device such as the one used by Salzer should be installed to prevent the exhaust gases from being poured out into the operating rooms.

Measures to Prevent Explosions due to Static Spark Within the Machines—1 Realizing that the bare rubber rebreathing bag as it is being used at the present time is very dangerous, we recommend (a) the trial of a small quantity of radioactive substance within the bag, and (b) if the foregoing method does not absolutely prevent charges from accumulating on the bag, replacement of the bag with the manometric device described.

2 Inspect the check valve admitting gases into the mixing chamber weekly to be sure that the valve and the valve seat are clean and dry.

Tests—During the cold months of the year, carry out an occasional test with a gold leaf electroscope to be assured that the system is actually eliminating the danger from static electricity.

Prof N H Williams of the Physics Department of the University of Michigan and Mrs Laura Davis-Dunston, instructor in anesthesia and chief anesthetist at the University Hospital, helped in the preparation of this paper.

THE VOLUME OF BLOOD FLOW PER MINUTE THROUGH THE LUNGS FOLLOWING COL- LAPSE OF ONE LUNG BY OCCLUSION OF ITS BRONCHUS

EXPERIMENTAL OBSERVATIONS¹

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The effect of atelectasis¹ of a lung on the pulmonary blood circulation became particularly interesting with the introduction of pneumothorax in the treatment for certain types of pulmonary tuberculosis. The significance of this relationship has increased in importance with the development of thoracic surgery, because there are few, if any, surgical procedures within the thoracic cavity or involving the thoracic wall that do not affect the expansion of the lungs. In spite of many experimental studies, however, there is no uniform agreement as to the exact nature of the resulting circulatory changes. Different investigators have arrived at conclusions that are diametrically opposed to each other, and the present status of knowledge is at best confusing and non-convincing.

The contradictory results are in part due to the fact that so far it has not been possible to determine by direct measurement the amount of blood that passes through a lung. Indirect methods offered the only means for the study of this problem, and the methods that have been used are varied and in some instances based on concepts now known to be erroneous.

Other causes for confusion can be traced to the several experimental procedures that have been used. Some writers have described the circulatory changes that accompany bronchial occlusion, others, the circulatory effects of a closed pneumothorax, and still others, the effects of an open pneumothorax. Whereas total or partial collapse of a lung may result from all of these procedures, the effect on the pulmonary

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1 The term "atelectasis," is used in this paper to denote diminished pulmonary expansion and not a state of complete collapse of the pulmonary alveoli. The term, "apneumatoxis," suggested by Coryllos and Birnbaum (Obstructive Massive Atelectasis of the Lung. Arch Surg 16:501 [Jan] 1928) more accurately describes this latter condition.

circulation, theoretically at least, may be quite different, because the physiologic alterations associated with each of these conditions are not the same. When a primary bronchus is totally occluded, collapse of the corresponding lung results from absorption of the trapped gases. As the gases are absorbed, the lung shrinks and eventually comes to occupy a much smaller portion of the thoracic cavity. The corresponding half of the diaphragm moves upward, and the mediastinum is pulled over to fill up the additional space. The elevation of the diaphragm and the displacement of the mediastinum follow readily, because both are yielding structures. The thoracic wall, on the other hand, is rigid and cannot be sucked inward. Under these conditions, the lung collapses toward the wall of the chest, and the pressure that is developed in the pleural space on the side of collapse during inspiration is probably more negative (i. e., unless the mediastinum can move over far enough to equalize the pressure) than it was under normal conditions.

In closed pneumothorax and open pneumothorax the lung collapses toward the mediastinum, and both of these conditions are accompanied by a decrease in the negative intrathoracic pressure and a shifting of the mediastinum to the opposite side of the thorax. In this way serious impairment of the expansion of the "opposite" lung in the closed half of the chest may accompany the reduced expansion of the lung on the side of pneumothorax. Attention was directed to this effect on the opposite lung by Bruns² in 1912, more recently Graham³ has proved it to be true by animal experimentation. This is an important consideration, because, as will be brought out later, some of the methods that have been used to estimate pulmonary blood flow are based on the assumption that in the presence of a unilateral open or closed pneumothorax the expansion of the contralateral lung is normal, or even increased.

In closed pneumothorax, the lung is compressed, and when the mediastinum is sufficiently rigid or sufficiently fixed by adhesions to prevent compression of the opposite lung, the intrapleural pressure on the side of pneumothorax can be raised to such a degree that it will exceed atmospheric pressure even at the height of inspiration. These are well known facts. I have repeated them here merely to illustrate the necessity of distinguishing between the effects of compression and atelectasis when studying the changes in the pulmonary circulation that accompany a closed pneumothorax.

2 Bruns, O. Untersuchungen über den respiratorischen Gaswechsel bei Erkrankungen der Lunge und der luftzuführenden Wege, *Deutsches Arch. f. klin. Med.* **107** 468, 1912.

3 Graham, E. A., and Bell, R. D. Open Pneumothorax. Its Relation to the Treatment of Empyema. *Am. J. M. Sc.* **156** 839, 1918.

These important physiologic changes must be kept in mind when one attempts to evaluate the experimental evidence that has been accumulated by others. If it is not known to what extent the expansion of a "collapsed" lung has been impaired, one cannot know accurately what is meant by the term "collapse." It is of equal importance to know also whether or not the expansion of the opposite lung has been affected. In general, it may be said that under normal conditions pulmonary expansion is dependent on the amount of negative intrathoracic pressure that is developed during inspiration. The importance, then, of changes in intrathoracic pressure cannot be overlooked.

The experiments of previous authors are not always specific in these important details. For some, "collapse" and "pneumothorax" are synonymous, and many overlook the effect of a closed or open pneumothorax on the expansion of the opposite lung.

Impressed primarily by the confusion that has arisen from the use of the term "collapse" in what might be called a qualitative sense, it occurred to me that a method which permitted quantitative measurement of the expansion and circulation of each lung separately would offer an excellent means for the study of the effect of atelectasis on pulmonary blood flow. In this communication, I am reporting the results of such a study. Complete collapse (apneumotosis) of one lung (either the right or left) has been produced in anesthetized dogs without restricting the breathing of the opposite lung, and the volume of pulmonary blood flow per minute through each lung separately has been measured before and after collapsing the lung. The results have consistently shown that the pulmonary circulation is strikingly decreased in a lung that has been rendered completely airless by occlusion of its bronchus. The knowledge and experience gained have led me to believe that the method can be used to study the pulmonary circulation in association with varying degrees of compression of the lung, and experiments of this character are now being considered.

HISTORICAL REVIEW

Lung Collapsed by Bronchial Occlusion—Loewy and von Schrotter⁴ introduced a lung catheter with a rubber balloon attached to one end into a branch bronchus or one main bronchus of man. By inflating the balloon, they were able to cut off completely the corresponding part of a lung or a whole lung, from the rest of the bronchial tree. They found that a considerable portion of one lung could be deprived

⁴ Loewy, A., and von Schrotter, H. Untersuchungen über die Blutcirculation beim Menschen, *Ztschr f exper Path u Therap* 1 197, 1905

of its ventilation without necessarily causing a decrease in the oxygen content of the arterial blood. In these experiments they assumed that the blood from the unventilated lung would be venous and should cause an increased unsaturation of the arterial blood. The fact, however, that the saturation of the arterial blood was unchanged, or only slightly reduced, suggested that the blood flow through the unventilated lung tissue was decreased.

Hess⁵ estimated the oxygen content of the arterial blood in a series of rabbits and then obstructed the primary bronchus of the left lung by introducing a tampon cannula and inflating a small rubber balloon which was attached to its end. Just as Loewy and von Schrotter had done before, he reasoned that after bronchial occlusion the arterial blood would be a mixture of venous blood (with low oxygen content) from the blocked lung and arterial blood (with high oxygen content) from the breathing lung. Hess assumed that under normal conditions the flow of blood through the left lung is one-third less than that through the right. Assuming further that the normal fraction of blood passed through the left lung after its bronchus was occluded, he calculated what the oxygen content of the arterial blood should be from the control arterial oxygen content⁶ and from the oxygen content of the venous blood after blocking. He found that the oxygen content of the arterial blood was approximately what he estimated it to be, and concluded that occlusion of a primary bronchus does not destroy the circulation in the corresponding lung, that approximately as much blood goes through after occlusion as before. The animals breathed air in all experiments, and observations were not made later than from five to ten minutes after bronchial occlusion. Autopsy never revealed a lung that was completely collapsed.

Adams and Morris⁷ noted a marked fall in the oxygen saturation of the arterial blood of dogs after occlusion of the main bronchus of the left lung. Administration of oxygen rapidly raised the arterial saturation to normal. This return of the arterial saturation to normal with one main bronchus occluded would not have been possible if blood were still circulating through the blocked lung. The observation suggested that the diminished saturation which followed bronchial occlusion

5 Hess, R. Ueber die Durchblutung nicht atmender Lungengebiete, *Deutsches Arch f klin Med* **106** 478, 1912.

6 In this calculation the oxygen content of the blood from the breathing lung (right lung) is assumed to be the same as the control arterial oxygen content. The formula from which the calculation is made is given in the paragraph which describes the experiments of Weiss.

7 Adams, D K, and Morris, N. Anoxaemia and the Administration of Oxygen, *J Physiol (Proc Physiol Soc)* **54** 102-104, 106-107, 1921.

was primarily due to insufficient oxygenation of the venous blood in the functioning lung (the animals were breathing air), and that the circulation in the occluded (collapsed) lung was severely impaired

Le Blanc⁸ estimated the oxygen content of the arterial and venous bloods before and after occlusion of one main bronchus and before and after the induction of a one-sided closed pneumothorax. In the first experiments, the bronchus was blocked by inflating a small rubber balloon which was attached to the end of a flexible catheter. Experiments were made on dogs, cats and rabbits during the inhalation of air. He found that shutting off one lung from breathing by occluding its bronchus was regularly followed by a significant fall in arterial oxygen content. Assuming that the blood which passed through the functioning lung was normally oxygenated, Le Blanc attributed the fall in oxygen content to the unarterialized blood from the blocked lung and concluded that the circulation in the blocked lung did not appreciably vary from the normal. Le Blanc stated, however, that at autopsy the lungs of these animals were always found to be inflated.

Andrus⁹ produced collapse of the left lung in dogs by ligating the primary bronchus and studied the circulation through the lungs before and after ligation. The total volume of blood per minute was determined by measuring the carbon dioxide output per minute and dividing this figure by the difference between the carbon dioxide content of the venous and arterial bloods. The average total volume of blood per minute of nine animals before operation was found to be 2,350 cc. One-half hour after operation, the average total flow was calculated from the average pulse volume before operation (191 cc) and the average pulse rate after operation (141) and found to be 2,680 cc, an increase of 14 per cent over the preoperative figure. One-half hour after operation, he found the average flow through the unblocked lung to be 1,830 cc, and subtracting this from the calculated total flow concluded that 850 cc, or only 31 per cent of the entire cardiac output, was flowing through the collapsed lung. Twenty-four hours later, he calculated a further decrease to 28 per cent and on the thirty-first day a decrease to 8 per cent.

8 Le Blanc, E. *Respiratorischer Gasaustausch und Lungendurchblutung unter normalen und krankhaften Zuständen der Atmungsorgane. Untersuchungen am arteriellen und venösen Blut von Mensch und Tier*, Beitr. z. Klin. d. Tuberk. **1** 21, 1922.

9 Andrus, W. DeW. *Observations on the Cardiorespiratory Physiology Following the Collapse of One Lung by Bronchial Ligation*, Arch. Surg. **10** 506 (Jan.) 1925.

Coryllos and Birnbaum¹⁰ produced experimental obstructive atelectasis and also experimental pneumonia in dogs and studied the lungs both by roentgenologic and histologic examination after intrajugular injections of iodized oil and india ink. They found that the iodized oil penetrated into the finer branches of the pulmonary artery and rendered them clearly visible in the x-ray pictures, but did not pass through the capillaries to the left side of the heart. No differences were apparent in roentgenograms between the affected and healthy lobes, other than dilatation of those branches of the pulmonary artery that supplied the atelectatic and consolidated parts. The dilatation was attributed to obstruction in the capillaries.

The india ink was injected under similar experimental conditions, but, in contrast to the iodized oil, readily went past the arterioles and penetrated the capillaries of the alveolar walls. The ink, just as the oil, was found to be distributed throughout both the affected and normal lobes. Striking differences, however, were noted in the number, size and shape of the injected capillaries of the atelectatic and consolidated areas. Coryllos and Birnbaum related these to the degrees of collapse of the corresponding alveoli and concluded that the capillary circulation is impaired in both atelectasis and pneumonia, and that the impairment is "due to, and regulated by, the degree of collapse of the alveoli."

Bruns came to the same conclusion in 1912. In that year, in a discussion of the pulmonary circulation in breathing and atelectatic lungs,¹¹ he said

Es ist also der Beweis erbracht, dass die Durchblutung normal ausgedehnter Lungen grosser ist als die kollabierter atelektatischer Lungen, ebenso wie ja auch die Blutmenge, die sich in einem gegebenen Augenblick in ausgedehnten, atmenden Lungen befindet, nach meinen Untersuchungen grosser ist als die in kollabierten. Je intensiver der Lungenkollaps, je ausgesprochener die Luftleere der Alveolen, desto kleiner ist die Blutmenge und die Stromgeschwindigkeit. Die Art der Ausschaltung der Atemfunktion spielt keine Rolle.¹² (It has been proved that a greater amount of blood passes through normally distended lungs than through collapsed atelectatic ones, likewise, according to my studies the amount of blood present in the lungs at a given moment is greater when they are distended in respiration than when they are collapsed. The more intense the collapse of the lungs, the less is the amount of air in the alveoli, and the less is the amount of blood and its velocity. The type of exclusion of the respiratory function does not play a rôle.)

10 Coryllos, P. N., and Birnbaum, G. L. The Circulation in the Compressed Atelectatic and Pneumonic Lung (Pneumothorax-Apneumatoses-Pneumonia), *Arch Surg* **19** 1346 (Jan.) 1929.

11 Bruns, O. Die Blutzirkulation in atmenden und atelektatischen Lungen. *Deutsche med. Wchnschr.* **39** 101, 1913.

12 Bruns' experiments are described in the section on "Lung Collapsed by Closed Pneumothorax," p. 231, this issue.

These studies of Coryllos and Birnbaum are interesting, but they do not give any information as regards the amount of blood that was circulating through the atelectatic and consolidated lobes during life. The histologic evidence cited, however, indicates that after death the atelectatic and consolidated areas contained less india ink than the expanded parts.

Lung Collapsed by Closed Pneumothorax —Bruns² studied the oxygen and carbon dioxide contents of both the arterial and the venous blood of rabbits, first, with the pleural cavities intact, secondly, after the production of a one-sided open pneumothorax and thirdly, after converting the open pneumothorax into a closed pneumothorax. He noted that open pneumothorax was regularly accompanied by a decrease in the oxygen contents and an increase in the carbon dioxide contents, but that both of these values immediately returned almost to normal when the chest was closed. This occurred even though the expansion of the atelectatic lung on the side of pneumothorax did not return to normal for about three days. The recovery of these values when the lung on the side of pneumothorax was still collapsed indicated, Bruns thought, that the changes could not have resulted from an admixture of imperfectly aerated blood from the collapsed lung. He concluded that the pulmonary circulation in the collapsed lung (lung on side of pneumothorax) was considerably reduced, and attributed the decrease in oxygen content and the increase in carbon dioxide content to a deficient ventilation of the opposite lung. Bruns maintained that when an opening in the thoracic wall is sufficiently large, the expansion of the opposite lung is impaired by a moving over of the mediastinum during inspiration, furthermore, that the emptying of the opposite lung during expiration is also imperfect, because the mediastinum now absorbs some of the pressure that results from collapse of the thoracic wall and elevation of the diaphragm by shifting back again to the side of the pneumothorax.

In other experiments, Bruns¹³ estimated separately the colorimetric value of the blood that is present in the right and left lungs of rabbits, first under normal conditions and then in the presence of a one-sided open or closed pneumothorax. He found that normally the amount of blood that is present in the right lung is to the amount in the left lung as 3:2. After the production of pneumothorax, the readings indicated consistently that a lung in the collapsed position contains less blood than it does in the position of natural expansion. Bruns also studied the

¹³ Bruns O. Ueber die Blutzirkulation in der atelektatischen Lunge, Deutsches Arch. f. klin. Med. **108** 469, 1912.

unit volume of blood flow through the lungs before and after the creation of a unilateral open, or closed, pneumothorax. He accomplished this by perfusing the lesser circulation with defibrinated blood through canulas which had previously been tied in the pulmonary artery and left ventricle. The cardiac output was taken as an index of the amount of blood passing through the pulmonary vessels. The output of the left ventricle was always lower after pneumothorax had been produced.

Bruns¹⁴ concluded that the manner in which collapse was produced made no difference. He applied his results with equal importance to atelectasis from pneumothorax, pleural effusions, pleural thickening and bronchial occlusion. He attributed the diminished circulation to an increased vascular resistance resulting from the winding and coiling of the pulmonary vessels and also to a possible vasoconstrictor effect.

Cloetta¹⁵ recorded the pressure changes in the pulmonary artery, right ventricle and carotid artery during the different phases of respiration, in dogs, cats and rabbits. He controlled the expansion of one or both lungs artificially by negative pressure in a plethysmograph and observed a fall in carotid pressure and a rise in pulmonary pressure whenever the lungs were inflated beyond the first one fourth or one third of the inspiratory phase. These changes were accompanied by a decrease of the systolic pressure and an increase of the diastolic pressure within the right ventricle. Cloetta also estimated the amount of blood in the lungs during the different respiratory phases from microscopic sections, and found that the amount of blood was less in the expanded lung than in the collapsed lung. As a result of his studies, he concluded that the pulmonary circulation is least at the height of inspiration, much better during expiration and best at the beginning of inspiration. Cloetta attributed the impairment of the blood flow during the latter half of inspiration to a stretching and narrowing of the pulmonary vessels. During the first part of inspiration, he believed that both the length and the cross-section of the vessels were increased. It is worthy of note here that he attributed the favorable influence of pneumothorax and thoracoplasty in pulmonary tuberculosis to an optimal flow of blood in the compressed lung.

White and Gammon¹⁶ studied the fate of particles of fat that were introduced intravenously into the pulmonary blood stream of rabbits.

14 Bruns (footnotes 11 and 13)

15 Cloetta, M. In welcher Respirationsphase ist die Lunge am besten durchblutet? *Arch f exper Path u Pharmacol* 70 407, 1912

16 White, W. C., and Gammon, A. M. Some New Features of Interest about the Pulmonary Circulation and the Fate therein of Intravenously Introduced Fats, *Tr Nat A Prev Tuberc*, Tenth Annual Meeting, 1914, pp 215-220

after the production of a unilateral artificial pneumothorax. They found that all the fat, save a very little which lodged at the hilus of the lung on the side of pneumothorax, went into the opposite lung. They do not mention either the type or the severity of the pneumothorax that was created, nevertheless, the observation suggests that under the conditions of their experiments an unknown degree of collapse, or compression of a lung, was associated with a severe impairment or complete obliteration of its blood supply.

Brauer¹⁷ maintained that the circulation through a lung that has been partially collapsed by pneumothorax, or thoracoplasty is slowed by stasis, and furthermore, that the increase in the blood flow through the opposite lung is slight.

Le Blanc⁸ found that a unilateral closed pneumothorax was regularly followed by only a slight oxygen deficit of the arterial blood, and concluded from this observation that the circulation in a lung that has been compressed by pneumothorax is considerably reduced.

Dock and Harrison¹⁸ studied the flow of blood through the lungs of rabbits before and after the production of a one-sided closed pneumothorax. Studies were made at intervals of from one hour to five days after the introduction of air into the right pleural cavity. The volume of flow of blood per minute was estimated from measurements of oxygen consumption and oxygen content of arterial and venous blood samples. The proportion of blood passing through the lung on the side of pneumothorax was calculated by subtracting the blood flow through the breathing lung from the total blood flow. Dock and Harrison found that immediately (from one to two hours) after the production of pneumothorax the flow through the "collapsed" lung was slightly more than half of the total flow, whereas after from three to five days it was less than one fifth of the total flow.

In experiments on rabbits during the inhalation of oxygen, Weiss¹⁹ computed the relative amounts of pulmonary circulation through the two lungs after a unilateral closed, and after an open pneumothorax. The computation was based on the obvious assumption that arterial blood from the carotid artery is a mixture of blood from both the right and the left lungs. Weiss reasoned that the character of the blood returning to the left side of the heart from the lung on the side of

17 Brauer, L. Ueber die operative Behandlung der Lungentuberkulose, Deutsche med. Wchnschr. **47** 548 1921.

18 Dock, W., and Harrison, T. R. The Blood Flow Through the Lungs in Experimental Pneumothorax, Am. Rev. Tuberc. **10** 534, 1925.

19 Weiss, R. Ueber die Durchblutung der Kollaps-lunge beim experimentellen Pneumothorax, Ztschr. f. d. ges. exper. Med. **53** 138 1926.

pneumothorax must necessarily be venous, and when the saturation of the mixed arterial blood did not fall below 90 per cent, he assumed that the decrease in saturation was due entirely to the venous blood that was returning from the "collapsed" side, and that the circulation through the "collapsed" lung was very small. Weiss did not think it conceivable that a high degree of saturation of the arterial blood could be maintained if venous blood was coming from the "collapsed" lung in large amounts. When the saturation of the arterial blood fell below 90 per cent, he assumed that the expansion of the opposite lung had been affected, and that the decrease was due, not only to venous blood from the "collapsed" lung on the side of pneumothorax, but also to venous blood from the unaerated portions of the lung on the opposite side. Weiss calculated the value of X and Y from the two formulas $X + Y = 100$ and $AX + VY = M(X + Y)$, in which A is the per cent of saturation of the arterial blood from the breathing lung, V the per cent of saturation of the venous blood from the collapsed lung, M the per cent of saturation of the mixed blood from the carotid, X the per cent of total pulmonary circulation through the breathing lung, and Y the per cent of total pulmonary circulation through the collapsed lung. The value of A was assumed to be 102.1 per cent. Weiss found that the pulmonary circulation through the lung on the side of pneumothorax was strikingly small in rabbits. In several experiments it was less than 12 per cent of the total pulmonary circulation.

In contrast to these results, Weiss found in similar experiments on dogs that considerable amounts of blood (up to 70 per cent of the total cardiac output) may pass through the nonaerated parts of the lungs. This calculated result was due to the marked decrease in the percentage of saturation of the arterial blood which followed production of a pneumothorax in these animals. As already indicated, Weiss attributed this conspicuous decrease to a shifting of the mediastinum and partial collapse of the opposite lung.

In several experiments, Weiss measured the oxygen absorption of his animals in addition to the arterial and venous oxygen contents and calculated the cardiac output per minute according to the Fick formula. He found that in the majority of instances the cardiac output was diminished.

Peters and Wolley²⁰ injected carbon particles (lamp black) into a vein of the ear of a rabbit after the induction of artificial pneumothorax. They found that the lung on the side of the pneumothorax filtered out

²⁰ Peters and Wolley, cited from Lilienthal, H. *Thoracic Surgery*, Philadelphia, W. B. Saunders Company, 1926, vol. 2, p. 325.

a smaller quantity of carbon, and took this as evidence that a smaller amount of blood circulated through it than through the opposite lung

In more recent studies on anesthetized dogs, Andrus and Wilson²¹ found that a closed pneumothorax of moderate size was accompanied by a 25 per cent increase in the amount of blood circulating through the lungs per minute, whereas pneumothorax of a larger size reduced the circulation through the lungs to 26.5 per cent below its resting value. The amount of blood flowing through the lungs per minute was calculated by dividing the oxygen consumption per minute by the difference between the arterial and venous oxygen contents.

Lung Collapse by Open Pneumothorax—Sackur²² produced an open pneumothorax on one side in five rabbits and one dog and measured the oxygen content of the arterial blood before and after the pleura was opened. He found that the oxygen content of the arterial blood decreased 50 per cent after creation of a right-sided pneumothorax. The change after a left-sided pneumothorax was similar, but less pronounced. Assuming that the ventilation of the lung opposite to the side of pneumothorax was increased, and furthermore, that as a result of this increased ventilation the blood passing through the opposite lung was better oxygenated, Sackur calculated the flow of blood through the lung on the side of pneumothorax, and found that it was always greater than the normal figure.

Sauerbruch²³ also expressed the belief that in a one-sided open pneumothorax the inactive, collapsed lung receives the greater part of the pulmonary blood supply. Reasoning purely on physical grounds, he stated that when the pressure in one pleural cavity approaches the pressure within the corresponding lung, the pulmonary vessels dilate and offer less resistance to the passage of blood. The blood from the collapsed lung is returned to the left side of the heart with a low oxygen content, and anoxemia and dyspnea result.

Mention has already been made of the experiments of Bruns²⁴ and Weiss¹⁹. In contrast to Sackur, both of these authors concluded from their experiments on rabbits that the amount of circulation in a lung collapsed by open pneumothorax was considerably reduced.

21 Andrus, W. DeW. and Wilson, J. D. The Effects of Closed Pneumothorax and Phrenicotomy on the Cardiorespiratory Function, *Arch. Surg.* **19** 1205 (Dec.) 1929.

22 Sackur. Zur Lehre vom Pneumothorax, *Ztschr. f. klin. Med.* **29** 25, 1896. Weiteres zur Lehre vom Pneumothorax, *Virchows Arch. f. path. Anat.* **150** 151 1897.

23 Sauerbruch, F. Zur Pathologie des offenen Pneumothorax und die Grundlagen meines Verfahrens zu seiner Ausschaltung. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **13** 399 1904.

24 Bruns (footnotes 2 and 13).

Yates,²⁵ who has given much thought to this subject, said that "maximum unit volumes of blood are delivered to unit volumes of lung when the lung is in a position of incomplete deflation corresponding to reduction but not to abolition of intrapleural negative pressures"²⁶ He quoted the experiments of Cloetta in support of this opinion, and expressed the belief that one of the important factors in the therapeutic value of artificial pneumothorax and phrenemphraxis is the improved circulation (pulmonary) in the affected lung Yates attributed this hypothetical improvement of the circulation to a decrease in the peripheral intravascular resistance, which allows the heart to propel more blood

Willy Meyer,²⁷ in agreement with Yates, also accepts the evidence of Cloetta as probably indicating a hyperemia of the collapsed lung

Torek,²⁸ on the other hand, expressed the belief that the greatest amount of blood is to be found in the expanded lung, less in the collapsed lung and least in the compressed lung He said that the negative pressure which is responsible for expansion of the lung sucks in blood from the right side of the heart, and that when it is increased, as during inspiration, there is a consequent increase in the amount of blood sucked in, whereas when the negative pressure is abolished, as it is during expiration, the blood is driven out

Eggers and Kernan,²⁹ commenting on the virtues of artificial pneumothorax in certain well selected cases of acute pulmonary suppuration, stated that there is less circulation in a collapsed lung than in an expanded one "owing to collapse of the alveoli with corresponding diminution in the size of the capillaries"

METHOD

Dogs were used They were anesthetized by the intravenous injection of barbital sodium, which was dissolved in physiologic solution of sodium chloride and given in the proportion of 0.3 Gm drug per kilogram of body weight The preparation of the animals was similar to that originally reported by Churchill and Agassiz³⁰ and recently used by the author in an experimental study of the vagal

25 Yates, J. L. Rationale of Operations Helpful in Promoting Recoveries from Pulmonary Tuberculosis, *Arch Surg* **14** 369 (Jan) 1927, in discussion of papers on "Acute and Chronic Nontuberculous Bronchopulmonary Suppurative Lesions," *Arch Surg* **16** 312 (Jan) 1928

26 Yates (footnote 25, second reference)

27 Meyer, W. (footnote 25, second reference, p. 309)

28 Torek, F. (footnote 25, second reference, pp. 316-317)

29 Eggers, C., and Kernan, J. D. Acute Pulmonary Suppuration. Selective Action of Artificial Pneumothorax in the Treatment of this Disease, *Arch Surg* **16** 279 (Jan) 1928

30 Churchill, E. D., and Agassiz, A. A Method for Separating the Air Breathed by the Right and Left Lungs, together with the Effect of Pulmonary Circulatory Changes on this Divided Breathing, *Am J Physiol* **76** 6, 1926

control of breathing³¹ It was devised to separate completely the respirations of the two lungs and is shown in diagram in figure 1 When anesthesia was complete, the trachea was exposed through a midline incision in the neck and opened horizontally at a point about 2 inches (5 cm) above the sternal notch Two metal tubes, which were subsequently to divide the trachea into two separate

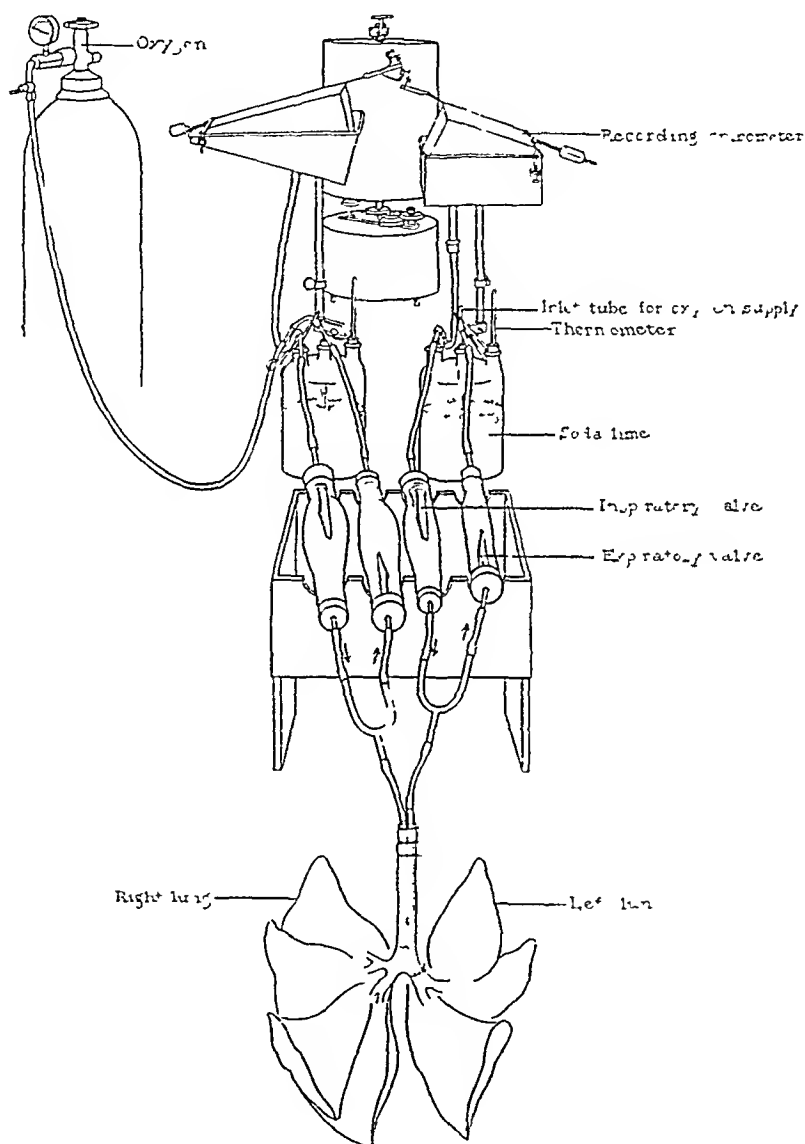


Fig 1—Diagrammatic view of the apparatus The lower part of the sketch, which shows the arrangement of the tubes which were used for the separation of breathing, was copied from the diagram published by Churchill and Agassiz (*Am J Physiol* 76 6, 1926) The sketch shows the two separate respiration systems and the manner in which the respiratory curves were made

compartments, were then inserted through the opening The tubes were 19 and 21 cm long and thin-walled, and both had an internal diameter of 7 mm The

³¹ Moore, R L A Study of the Hering-Breuer Reflex, *J Exper Med* 46 819, 1927

longer one was curved at one end to conform with the angle at which the bronchus unites with the trachea. It had in addition two rubber rings at the extreme end with a narrow groove in between for receiving the ligature, which subsequently fastened it in the bronchus. This tube was passed downward into one bronchus. The shorter tube was straight. It was passed down to the opposite bronchus, but did not enter it. When the tubes were in place they were temporarily anchored by a ligature around the trachea about $1\frac{1}{2}$ inch (3.7 cm) below the opening. The animal was then given artificial respiration through each tube separately and turned on the right or left side, depending on whether the left or right bronchus was to be cannulated. The chest was opened in the fourth intercostal space by an incision beginning 1 inch (2.5 cm) lateral to the edge of the sternum and extending around the chest for a distance of approximately 3 inches (7.6 cm) and the ribs were spread and held apart by a mechanical retractor. The lung was reflected anteriorly and the bronchus isolated. This was done almost entirely by blunt dissection to avoid cutting nerve fibers and reduce bleeding to a minimum. After placing a ligature of heavy silk behind the bronchus, the long cannula was manipulated into position and firmly ligated. Expansion of all lobes of the lung subsequent to this indicated that the correct position had been obtained. Before completely closing the thorax, the lungs were expanded to expel the air from the chest. Closure was accomplished by suturing the intercostal muscles. When closure was complete, artificial respiration was discontinued and the animal breathed naturally. The opening in the trachea was now closed by packing muscle into the space between the tubes and tracheal wall down to the "anchor" ligature and compressing the trachea and muscle against the tubes with two additional ligatures. This procedure completely separated the breathing of the two lungs. Each cannula was now connected with a separate closed respiration system, including inspiratory and expiratory valves, sodium lime for removing carbon dioxide and a small spirometer for recording oxygen absorption curves and changes in respiratory movement. All animals breathed from 90 to 95 per cent oxygen throughout the period of observation. As the oxygen was absorbed, it was replaced through an inlet tube as shown in the diagram.

Every experiment was begun with a series of control observations. The oxygen absorption, respiratory rate and respiratory depth (tidal air) of each lung were obtained from the kymographic tracings. Representative samples of respiratory tracings are reproduced in figure 2. The pulse rate was counted with the aid of a stopwatch. While the tracings were being made, samples of arterial and mixed venous blood were collected. The arterial blood was withdrawn from the femoral artery through a cannula or by puncture. The mixed venous blood was taken from the right side of the heart by means of a special cannula introduced into that chamber through a slit in the right external jugular vein³². The samples of blood were carefully protected from air and transferred immediately to oiled sampling tubes beneath oil and placed in the icebox until analyzed. The oxygen content of the samples was estimated by the Van Slyke and Neill³³ manometric method and the amounts of oxygen expressed in per cent by volume. All of the analyses were made in duplicate, and results which did not check within 0.5 per cent by volume were discarded.

32 Stewart, H. J. The Oxygen and Carbon Dioxide Contents of the Arterial and Mixed Venous Blood in Normal Intact Dogs, *J. Biol. Chem.* **62** 641, 1925.

33 Van Slyke, D. D., and Neill, J. M. The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J. Biol. Chem.* **61** 523, 1924.

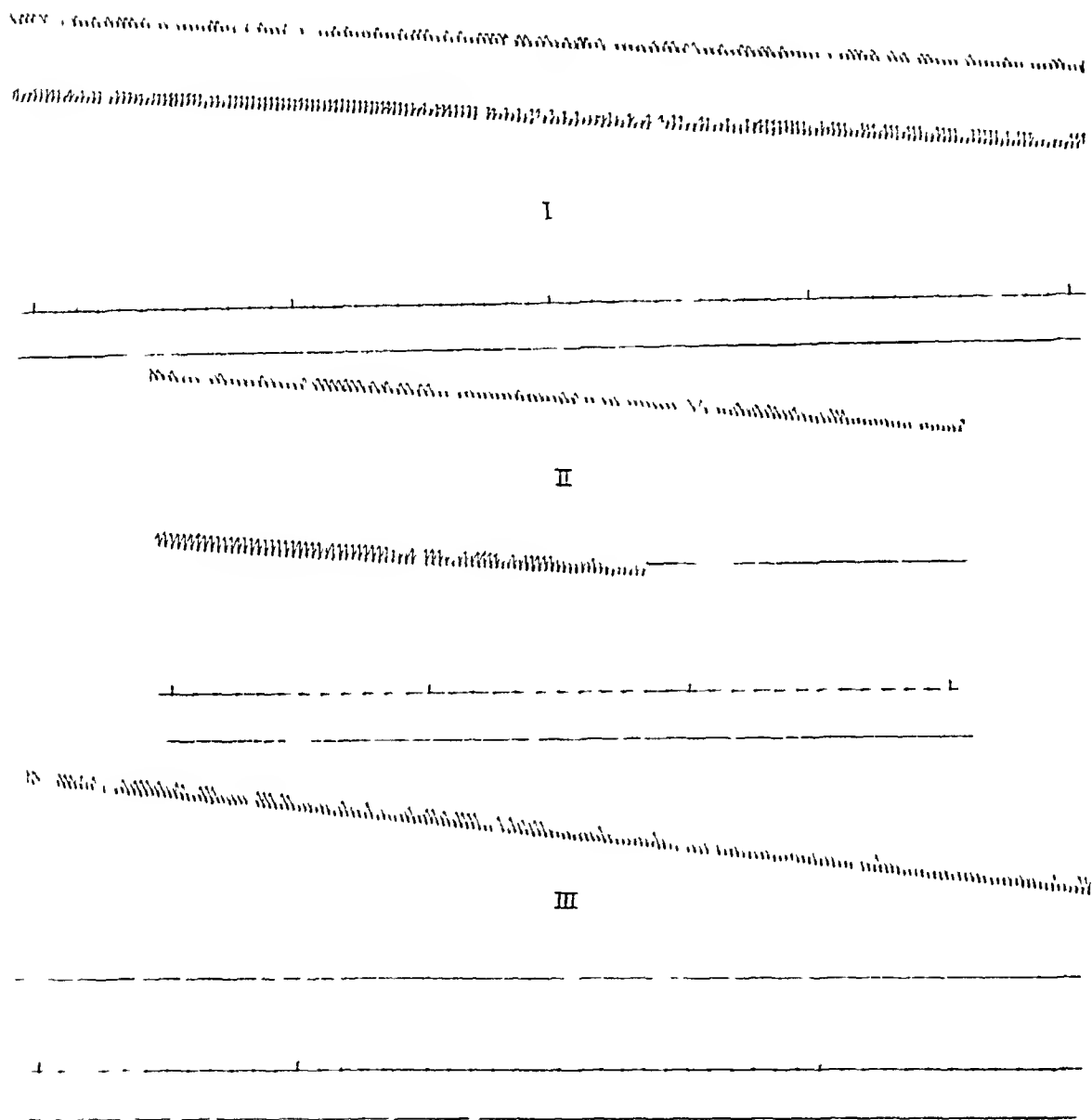


Fig 2—The respiratory tracings in experiment 7. The three sections were continuous and the upper and lower tracings were made by the right and left lungs respectively. In the upper tracing an excursion on the arc which is subtended by a chord 1 inch long represents a 231 cc change in the volume of the recording spirometer. In the lower tracing, written by a smaller spirometer, an excursion on the arc which is subtended by a chord 1 inch long represents a volume change of only 141 cc. Section A shows the control period, section B, the point at which the left bronchus was blocked and section C, the curve made by the right lung twenty minutes later. Time interval, five seconds.

The difference between the oxygen content of the arterial and of the mixed venous blood gives the amount of oxygen removed from the blood by the tissues or from the point of view of the lesser circulation the amount of oxygen taken up by the blood in passing through the lungs. With these one can calculate the total volume of blood flow per minute through the lungs according to the principle of Fick³⁴

$$\frac{\text{cc of oxygen removed per minute}}{\text{amount of oxygen absorbed by 1 cc of blood in passing through the lungs}} = \frac{\text{cc of blood passing through the lungs per minute}}{\text{cc of blood passing through the lungs per minute}}$$

TABLE 1—*Proportion of Oxygen Absorbed by Right and Left Lungs Respectively after Cannulation of One Main Bronchus and Complete Separation of the Breathing*

Experiment Number	Bronchus Cannulated	Oxygen Absorbed	
		By Right Lung, Per Cent	By left Lung, Per Cent
8	Left	56.2	43.8
7	Left	62.2	37.8
6	Left	60.6	39.4
20	Right	63.8	36.2
21	Right	64.5	35.5
2	Left	59.0	41.0
10	Right	60.6	39.4
11	Right	57.4	42.6
22	Left	57.1	42.9
14	Left	49.7	50.3
16	Left	56.7	43.3
17	Left	59.0	41.0
3	Left	60.4	39.6
1	Left	64.2	35.8
Average amount of oxygen absorbed by right lung in thirteen experiments (experiment 14 omitted)		60.1	
Average amount of oxygen absorbed by left lung in thirteen experiments (experiment 14 omitted)			39.9

If the amount of oxygen absorbed by each lung is measured separately, as it has been in my experiments, one can go further than this, and with the same formula estimate the volume of flow through each lung separately, provided that the oxygenation of the blood is the same in the two lungs. In the presence of normal lungs and adequate ventilation, one would hardly suspect this of being otherwise, still less so with an increased alveolar oxygen tension which is present during the inhalation of oxygen. There is additional evidence which indicates that this was true in my experiments. In every instance except one (experiment 14), the proportion of oxygen absorbed by the right and left lungs was approximately in the ratio of 3 : 2, a ratio which, as a result of observations made on fourteen different animals (table 1) I have come to regard as normal in dogs. Furthermore, in thirteen of the fourteen experiments, the oxygen content of the mixed arterial blood (femoral artery) was not found to vary to any appreciable extent from the oxygen content of the aerated blood (table 2). If the blood returning from one lung was incompletely oxygenated, this observation would not have been possible. The oxygen content of the aerated blood (oxygen

³⁴ Fick, A. Ueber die Messung des Blutquantums in der Herzventrikeln. Verhandl. d. phys.-med. Gesellsch. 2, 16, 1870.

capacity) was estimated after rotating the sample of blood in a flask for ten or fifteen minutes, during which time it was exposed to air at room temperature.

When these observations were completed, the airway to one lung was suddenly occluded by clamping the rubber tube connection between the cannula and respiration valves, and after a variable period of time all of the studies were repeated. The latter studies, however, were not made until the blocked lung was in a state of complete collapse, demonstrated in every instance by an autopsy which was performed immediately after the blood specimens were taken. The oxygen absorption of the patent lung now represents the total oxygen absorption, and one can calculate the total volume of blood flow from the formula already given. The blood flow through the patent lung is calculated likewise by assuming that the oxygen content of the arterial blood returning from it is maximal or equal to the oxygen content of the aerated blood. The truth of this assumption is scarcely questionable in the light of the increased ventilation of the patent lung (table 7) and the fact that its oxygen absorption at this time is increased over the control by the amount that was being absorbed by the opposite lung before its bronchus was occluded. The circulation through the collapsed lung is obtained by subtracting this amount from the amount that represents the total flow. In this way, the maximal amount of blood that could be in circulation through the collapsed lung was calculated. This method of calculating the blood flow through each lung separately was described by Dock and Harrison¹⁸. If it is assumed that the venous blood is not completely oxygenated in the aerated lung, the calculations would yield still larger values for the blood flow through the patent lung, and consequently smaller values for the flow in the collapsed lung.

EXPERIMENTAL WORK

The Relative Amounts of Blood Passing Through the Right and Left Lungs After Cannulation of One Main Bronchus and Complete Separation of the Breathing—The amount of oxygen absorbed by each lung separately was measured in fourteen experiments, and the experimental data are presented in tables 1 and 2. It will be noted that with one exception (experiment 14) the proportion of oxygen absorbed by the right and left lungs was approximately in the ratio 3:2. Excluding experiment 14, the percentage of oxygen absorbed by the right lung varied between 56.2 and 64.5, and averaged 60.1, whereas that absorbed by the left varied between 35.5 and 43.8, and averaged 39.9. I believe that these figures represent the normal ratio in dogs, not only for the oxygen absorbed by the right and left lungs, respectively, but also for the relative amounts of pulmonary blood flow. Evidence in support of this has already been given (see Method). The actual amounts of blood, expressed in cubic centimeters per minute, are given in table 2.

It was conceivable that the oxygen absorption of the lung on the side on which operation was performed might be impaired by the operative procedure either through some restriction of the movements of the thoracic wall or by some change resulting from the necessary manipulation of the lung. This possible traumatic factor was con-

TABLE 2—Effect of Collapsing One Lung on Volume of Blood Flow Through the Lungs

Experimental Number and Sex *	Date	Weight Kg	Time Minutes	Conditions	Oxygen Content			Oxygen Saturation		Arteriovenous Oxygen Difference		Oxygen Absorption			Volume of Blood Flow		
					Arterial Blood (Femoral Artery) Per Cent by Volume	Mixed Venous Blood (Right Side of Heart), Per Cent by Volume	Aerated Blood (Oxygen Capacity), Per Cent by Volume	Arterial, Per Cent	Mixed Venous, Per Cent	Total, Per Cent by Volume	Functioning Lung Per Cent by Volume	Right Lung, Cc per Minute	Left Lung, Cc per Minute	Total Cc per Minute	Through Right Lung, Cc per Minute	Through Left Lung, Cc per Minute	Total, Cc per Minute
♂ 8	1/4/29	11.6	3 20	Control	22.9	20.8	23.2	98.7	89.7	2.1		27.0	21.0	48.0	1286	1000	2286
			3 42	Left bronchus blocked													
			3 57	Left lung collapsed	22.5	18.4	25.0	90.0	73.6	1.1	6.6	63.5	0	63.5	962	587	1549
♂ 7	12/19/28	18.1	3 40	Control	17.5	15.8	18.5	94.6	85.4	1.7		58.0	35.2	93.2	3112	2070	5182
			3 52	Left bronchus blocked													
			4 12	Left lung collapsed	18.8	16.3	19.5	96.4	83.6	2.5	3.2	93.5	0	93.5	2922	818	3740
♂ 6	12/13/28	13.3	3 30	Control	19.5	14.1	19.7	99.0	73.1	5.1		17.3	30.8	78.1	927	601	1531
			3 49	Left bronchus blocked													
			4 17	Left lung collapsed	19.5	14.9	21.1	91.1	69.6	4.6	6.5	77.0	0	77.0	1185	189	1671
♂ 20	4/16/29	16.9	1 45	Control	20.5	18.3	21.5	95.3	85.0	2.2		11.1	23.3	61.1	1868	1059	2927
			4 55	Left bronchus blocked													
			5 55	Left lung collapsed	19.8	16.1	19.5	101.0	82.6	3.7	3.1	61.2	0	61.2	1800	0	1851
♂ 21	4/30/29	11.5	3 30	Control	21.0	19.0	20.9	100.0	91.0	2.0		21.9	13.7	38.6	1245	685	1930
			3 32	Left bronchus blocked													
			1 32	Left lung collapsed	20.1	15.8	20.9	96.1	75.6	4.3	5.1	34.9	0	34.9	681	128	812

2	♂	11/ 1/28	13 0	3 30	Control	13 8	11 8	15 1	91 1	78 1	2 0	39 8	27 7	67 5	1990	1385	3375
				3 40	Left bronchus blocked												
				1 55	Left lung collapsed	15 7	10 4	15 7	100 0	66 2	5 3	5 3	0	63 3	1194	0	1194
10	♀	1/16/29	12 6	3 55	Control	21 8	17 6	22 9	95 2	76 9	4 2	47 0	30 5	77 5	1119	720	1845
				4 07	Right bronchus blocked												
				4 22	Right lung collapsed	20 4	12 8	23 5	86 8	54 5	7 6	10 7	0	72 3	275	676	951
11	♀	1/23/29	12 0	4 40	Control	17 4	15 4	17 0	102 0	90 6	2 0	34 0	25 3	59 3	1700	1260	2960
				4 52	Right bronchus blocked												
				5 07	Right lung collapsed	15 9	12 2	18 0	88 3	67 8	3 7	5 8	0	60 0	588	1034	1622
22	♂	5/21/29	12 5	2 35	Control	16 1	13 1	16 0	100 0	81 9	3 0	28 8	21 6	50 4	960	720	1680
				2 17	Right bronchus blocked												
				3 02	Right lung collapsed	13 5	7 9	17 0	79 4	46 5	5 6	9 1	0	49 5	340	511	884
11	♂	2/20/29	9 5	3 25	Control	21 2	17 1	21 6	98 1	80 6	3 8	34 5	35 0	69 5	908	921	1829
				3 37	Right bronchus blocked												
				1 37	Right lung collapsed	20 4	14 9	22 0	92 7	67 7	5 5	7 1	0	76 3	313	1074	1387
16	♂	3/ 6/29	18 0	3 36	Control	19 1	16 6	18 9	102 6	87 8	2 8	46 6	35 6	82 2	1604	1271	2935
				3 40	Right bronchus blocked												
				1 10	Right lung collapsed	16 1	11 7	19 3	83 4	60 6	1 4	7 6	0	95 3	912	1254	2166
17	♀	3/13/29	13 5	2 20	Control	22 0	19 6	22 3	98 7	87 8	2 1	36 1	25 4	61 8	1517	1058	2575
				2 29	Right bronchus blocked												
				3 35	Right lung collapsed	20 0	13 5	22 9	87 3	59 0	6 5	9 1	0	64 8	308	689	997
3	♂	11/11/28	12 0	2 10	Control	20 0	19 0	20 1	99 5	94 5	1 0	27 5	18 0	45 5	2750	1800	4550
				3 27	Left bronchus blocked	Blood flow studies not possible because cannula for withdrawing mixed venous blood was incorrectly placed											
				5 00	Left lung collapsed											51 9	

Blood flow studies not possible because cannula for withdrawing mixed venous blood was in the superior vena cava, experiment was not completed

* In this table ♂ indicates male ♀ female

controlled by cannulating the left bronchus in some experiments and the right bronchus in others. The results were the same under both conditions.

The Changes in Pulmonary Circulation Following Collapse of the Left Lung—The left bronchus was totally occluded and the left lung rendered completely airless in six experiments. Estimations of the effect

TABLE 3—*Summary of Effect of Occluding Left Bronchus (Collapsing Left Lung) on Volume of Blood Flow Through Lungs**

Experiment Number	Duration of Bronchial Occlusion, Minutes	Degree of Change in Volume of Blood Flow		
		Total Per Cent	Right Lung, Per Cent	Left Lung Per Cent
8	17	—31.0	—25.0	—41.1
7	20	—32.0	—14.4	—60.5
6	29	+9.3	+21.6	—19.0
20	60	—43.5	—3.6	—100.0
21	60	—57.9	—47.1	—81.3
2	75	—64.6	—66.6	—100.0

* Increase is indicated by +, decrease by —. In every instance the "blocked" lung was completely collapsed (apneumatic) when these observations were made.

Macroscopic examinations were supplemented by microscopic examinations in experiments 6 and 7.

TABLE 4—*Proportion of Blood Passing Through the Right and Left Lungs Before and After Collapse of the Left Lung*

Experiment Number	Volume of Blood Flow During Control Period		Volume of Blood Flow After Collapse of Left Lung	
	Right Lung, Per Cent	Left Lung, Per Cent	Right Lung Per Cent	Left Lung Per Cent
8	56.2	43.8	62.0	38.0
7	62.2	37.8	78.1	21.9
6	60.6	39.4	70.8	29.2
20	63.8	36.2	100.0	0
21	64.5	35.5	84.2	15.8
2	59.0	41.0	100.0	0
Average	61.1	38.9	82.5	17.5

on blood flow in the different animals were made at intervals which varied from seventeen to seventy-five minutes after the bronchus was occluded. In every instance the volume of blood per minute through the left lung showed a substantial decrease (from 19 to 100 per cent), which was most pronounced after the longer intervals. The average decrease in volume of blood per minute through the left lung was 67 per cent. In five experiments (8, 7, 20, 21 and 2), the cardiac output and the flow through the opposite (right) lung likewise diminished but to a less extent. The latter observations showed a slight increase in

experiment 6 The proportion of blood passing through the right and left lungs during the control period averaged 61.1 and 38.9 per cent, respectively After collapse of the left lung the average percentage of blood passing through the right lung increased to 82.5, and that passing through the left decreased to 17.5 The actual values are shown in table 2 and the percentage changes in tables 3 and 4 In general, these results agree with those which were obtained by Loewy and von Schrotter,⁴ Adams and Morris,⁷ Andrus⁹ and Coryllos and Birbaum¹⁰ It is worthy of note that both Hess⁵ and Le Blanc,⁸ who concluded that the pulmonary circulation in a blocked lung was not decreased noted at autopsy that the lungs of their animals were inflated

The Changes in Pulmonary Circulation After Collapse of the Right Lung—These experiments were similar in every respect to those

TABLE 5—*Summary of Effect of Occluding Right Bronchus (Collapsing Right Lung) on Volume of Blood Flow Through the Lungs*

Experiment Number	Duration of Bronchial Occlusion Minutes	Degree of Change in Volume of Blood Flow		
		Total Per Cent	Right Lung Per Cent	Left Lung Per Cent
10	15	—48.1	—75.5	—6.9
11	15	—45.2	—64.8	—17.9
22	15	—47.4	—64.6	—24.4
14	60	—24.2	—65.5	—14.2
16	60	—26.2	—45.0	—1.3
17	66	—61.0	—80.0	—35.0

* Decrease is indicated by — In every instance the 'blocked' lung was completely collapsed (apneumatic) when these observations were made

Macroscopic examinations were supplemented by microscopic examinations in experiments 10, 14 and 16

reported under "Changes in Pulmonary Circulation Following Collapse of the Left Lung," with the one exception that the right lung was collapsed instead of the left The intervals of time allowed to elapse between bronchial occlusion and the second estimations of the volume of blood flow varied in this group from fifteen to sixty-six minutes Just as in the former series, all animals showed a conspicuous decrease in the volume of blood flow per minute through the collapsed lung The decrease varied from 45 to 80 per cent, averaging 65.9 just a trifle less than the corresponding figure for the left lung All animals likewise showed a noticeable decrease in cardiac output and a similar, though less striking, change in the volume of flow through the functioning lung

The change in the proportion of blood passing through the two lungs was equally as striking In these six experiments during the control period, the percentage of the cardiac output that passed through the right and left lungs averaged 56.8 and 43.2 respectively After

collapse of the right lung, these values were reversed to 33.2 for the right lung and 66.8 for the left. The experimental data are presented in tables 2, 5 and 6.

The Effect of Total Collapse of One Lung on the Ventilation of the Opposite Lung and on the Respiratory and Pulse Rates—These data are shown in table 7. As we expected, the depth of breathing of the opposite lung was consistently increased and the degree of increase was most marked after right-sided collapse. The effect on respiratory rate was variable. In three instances (experiments 7, 20 and 10), the rate showed practically no change. In one experiment (experiment 6) it decreased slightly, and in the other eight experiments it was regularly increased. The volume per minute of pulmonary ventilation of the

TABLE 6—*Proportion of Blood Passing Through the Right and Left Lungs Before and After Collapse of the Right Lung*

Experiment Number	Volume of Blood Flow During Control Period		Volume of Blood Flow After Collapse of Right Lung	
	Right Lung, Per Cent	Left Lung, Per Cent	Right Lung, Per Cent	Left Lung, Per Cent
10	60.6	39.4	28.9	71.1
11	57.4	42.6	36.3	63.7
22	57.1	42.9	38.5	61.5
14	49.7	50.3	22.6	77.4
16	56.7	43.3	42.1	57.9
17	59.0	41.0	30.9	69.1
Average	56.8	43.2	33.2	66.8

breathing lung, obtained by multiplying tidal air (expansion) by respiratory rate per minute, was conspicuously increased in all of the experiments, illustrating the remarkable degree to which one lung can compensate when the function of the other is destroyed. Under the conditions in my experiments, one lung (either the right or left) could easily do the work of two.

Usually the pulse rate did not vary, or the variation was so slight that it was not significant. This indicates that the striking decrease in cardiac output per minute which followed collapse of one lung was accompanied by a proportional decrease in the stroke output of the heart. Therefore, it would appear that experimental collapse of one lung during the inhalation of oxygen relieved the heart of part of its burden.

Postmortem Examination—After the final observations, each experiment was terminated by the intravenous injection of from 20 to 30 cc of a saturated solution of magnesium sulphate, and all animals were subjected to immediate autopsy. The cannula to the nonblocked lung was occluded before the thorax was opened. This prevented partial deflation of the lung when the negative intrathoracic pressure was

destroyed and afforded an opportunity to compare the sizes of the two lungs under controlled conditions. Histologic examinations were made in five experiments. The sections were fixed in formaldehyde, embedded in paraffin and stained with eosin and methylene blue. The pathologic changes were the same in all instances. The lung, the bronchus of which had been occluded during life (collapsed lung), was found to be only about one-third the size of the breathing lung. It was deep red,



Fig. 3—Photograph of the lungs from experiment 6. The left lung was airless, dark red, firm to palpation, heavy and sank in water. The right lung was expanded throughout the complete extent of all the lobes.

firm to palpation, heavy and rapidly sank in water. Its appearance resembled that of normal liver, and its cut surface freely exuded dark red blood. In striking contrast, the opposite lung was distended and of a normal pink appearance. The pleural cavity on the side of collapse regularly contained from 10 to 30 cc. of hemorrhagic fluid.

Sections of the collapsed lobes showed complete obliteration of the alveolar spaces. The alveolar septums were everywhere in intimate contact with each other, and the capillaries appeared to be congested.

with red blood corpuscles. Numerous mononuclear leukocytes were present in all the sections, and small foci of blood pigment were frequently observed.

A photograph of the lungs from experiment 6 is reproduced in figure 3, and photomicrographs of sections of the lungs from experiment 6 are shown in figures 4, 5 and 6.

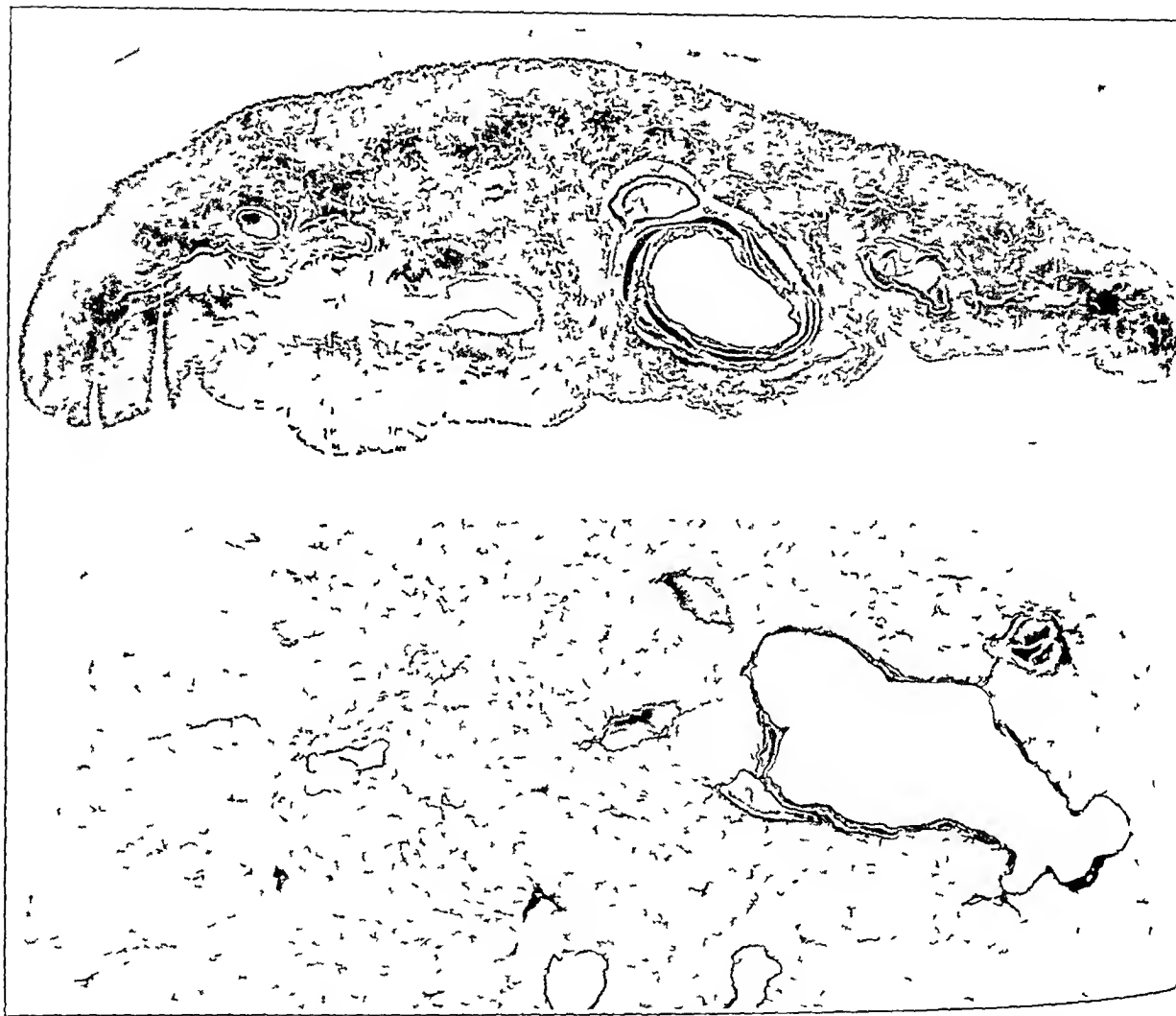


Fig. 4—Photomicrograph of sections of the upper lobes of the lungs from experiment 6. Reduced from a magnification $\times 10$. The upper picture shows complete obliteration of the alveolar spaces of the collapsed (left) lung. The right lobe (lower picture) is air-containing and presents a normal lung architecture.

The collapse of a lung which follows bronchial occlusion results from absorption of the gas that is trapped in the blocked alveoli. When the alveoli contain a high percentage of oxygen, this phenomenon occurs very rapidly, because the oxygen readily combines with the hemoglobin of the circulating blood. As the oxygen is removed, the alveolar walls

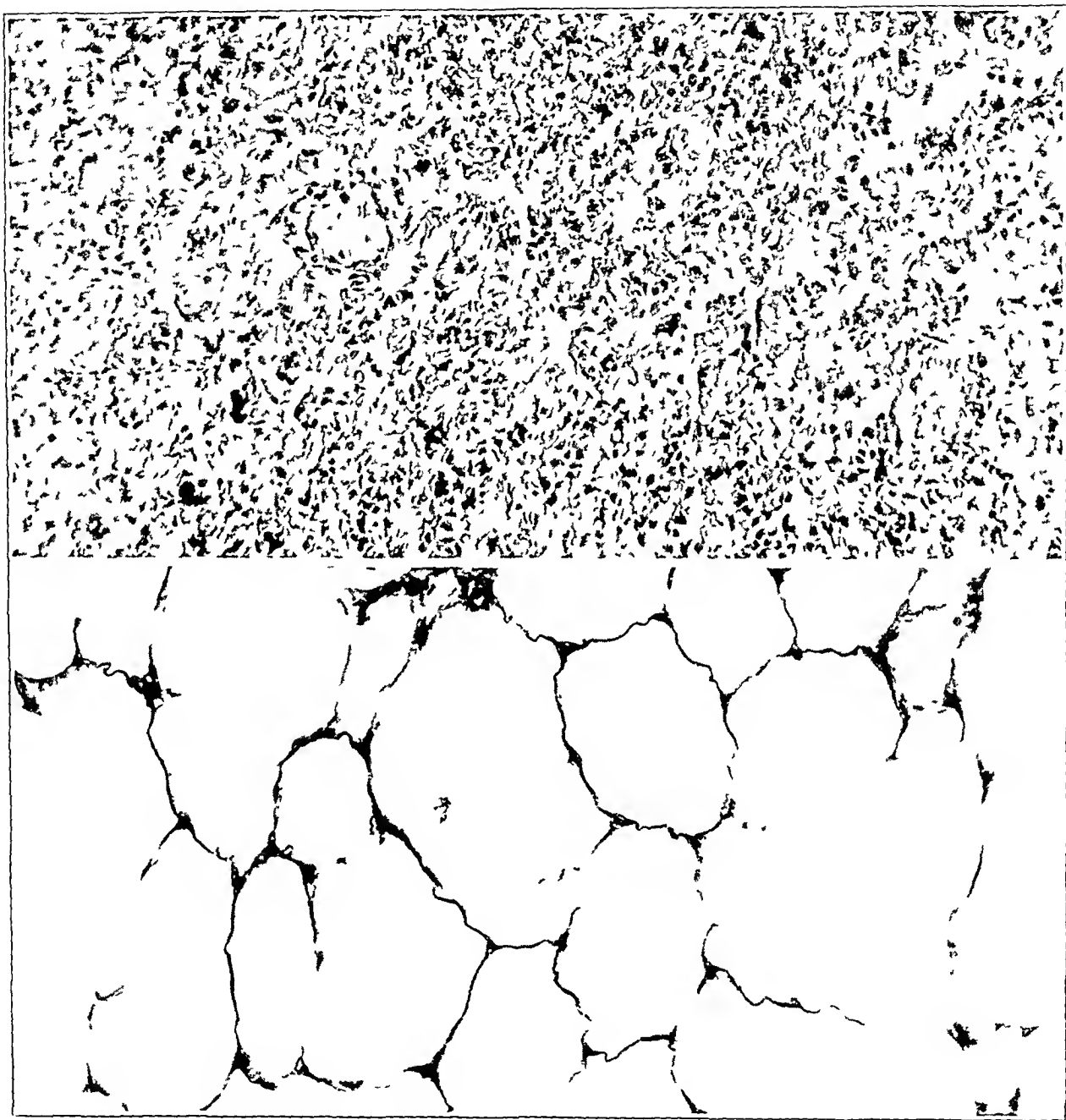


Fig 5—Photomicrograph of sections of the upper lobes of the lungs from experiment 6. Reduced from a magnification $\times 100$. In the upper picture (left lung) the alveolar septums are in intimate contact with each other and the capillaries are tortuous and engorged with red blood cells. The black specks which resemble bacteria are fragments of blood pigment. The lower picture (right lung) does not show any appreciable variation from normal.

shrink and fall together, and eventually the lung becomes airless. Deflation occurs much more slowly if a bronchus is occluded during the inhalation of air, because under these conditions the alveoli contain a large percentage of nitrogen with which gas the blood is normally saturated. These phenomena have been observed by Moore and Har-

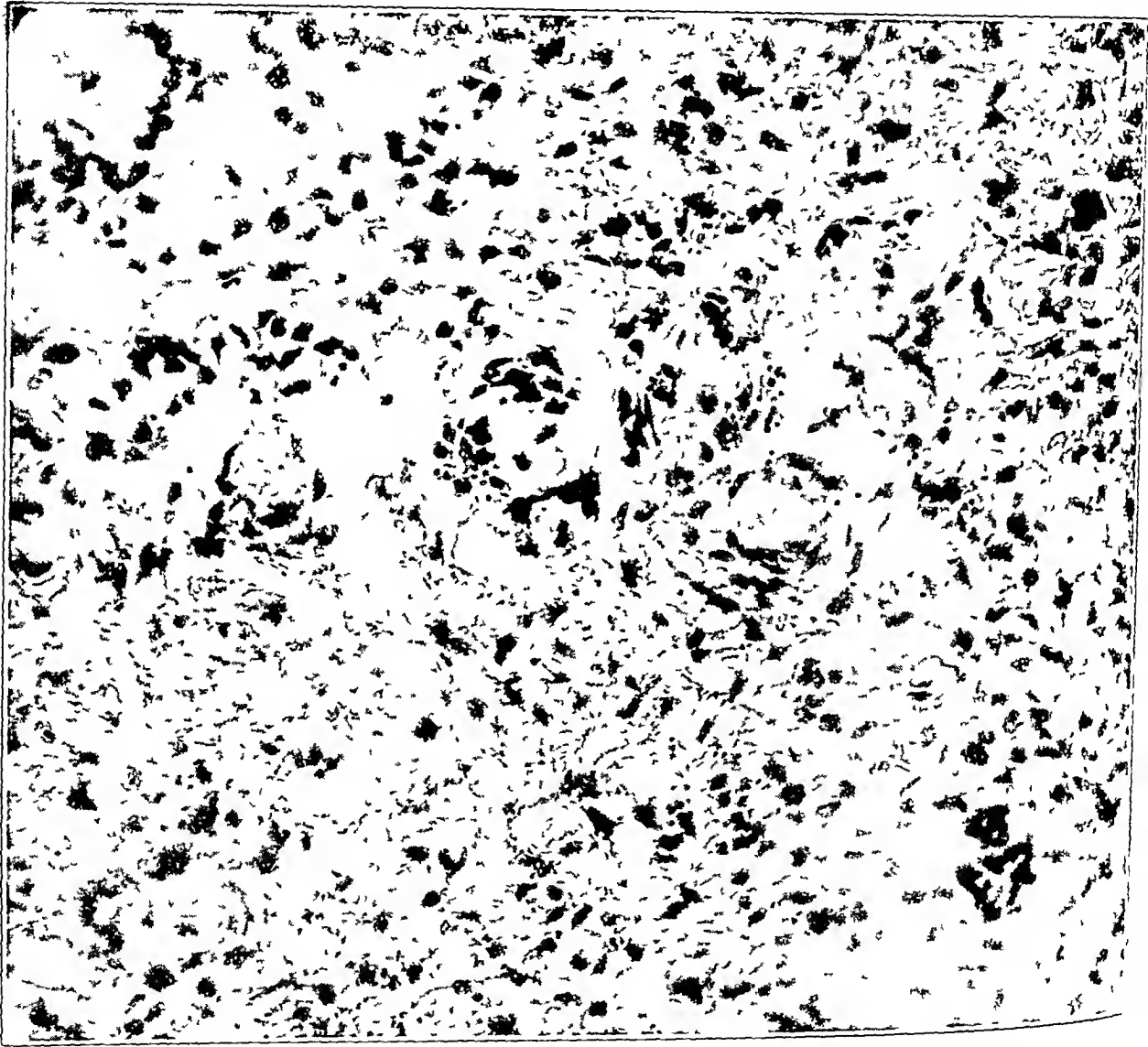


Fig 6—Photomicrograph of section of the left upper (collapsed) lobe from experiment 6. Reduced from a magnification $\times 400$. Here the engorgement of the capillaries is shown in greater detail.

1150N³⁵ when the chest was open and the animal was receiving artificial respiration. This mechanism for collapse was first described by Lichtheim³⁶ and was recently emphasized by Coryllos and Birnbaum¹.

35 Moore, R. L., and Harrison, T. R. Unpublished experiments.

36 Lichtheim, L. Versuche über Lungenatelektase. Arch. f. exper. Path. u. Pharmacol. 10: 54, 1878.

COMMENT

The lesser circulation is concerned primarily, it not entirely, with the absorption of oxygen and the elimination of carbon dioxide and heat. This is rendered possible by the alternate expansion and collapse of the lungs (pulmonary ventilation). Through this mechanism air is brought into close contact with the circulating blood; the alveolar supply of oxygen is repeatedly replenished, and the elimination of carbon dioxide is accelerated. The amount of oxygen that will be removed from the lungs by the blood in a unit of time (provided the supply is adequate) will largely depend on the amount of reduced hemoglobin with which the oxygen comes in contact. I know from clinical experience, and my experiments have demonstrated clearly that one healthy lung is sufficient to take care of the oxygenation of the blood. This can be done with greater ease and with less strain on the circulation when the alveolar oxygen tension is increased by the administration of oxygen. If the ventilation of one lung is severely impaired by pneumothorax, bronchial occlusion or consolidation, the supply of oxygen to this lung may be diminished to the point of being inadequate. Under such conditions the blood that leaves this lung will enter the systemic circulation with a low oxygen content, and anoxemia will result. If, however, a diminution in blood flow accompanies the decrease in ventilation and not an increase in flow, as maintained by some authors, anoxemia may not follow, or its degree will be less. Therefore, from the physiologic standpoint it is easier to conceive of a diminished pulmonary ventilation, which is accompanied by an increased pulmonary blood flow, working to the disadvantage rather than to the advantage of the organism, whereas simultaneous and proportionate decrease in both of these functions, such as occurred in my experiments, would be advantageous.

Furthermore, that a beneficial effect on a healing process would come from an increased venous blood supply, as maintained by Cloetta¹⁵ and Yates,²⁵ is open to question. In regard to the lung, it is not known to what extent venous blood shares the responsibility of nourishing lung tissue. That the bronchial supply is adequate for this is proved by the fact that necrosis of lung tissue does not follow ligation of the pulmonary artery.³⁷

This paper would not be complete without a discussion of the possible causes of the diminished pulmonary circulation in the collapsed lung. In this condition, in addition to the actual decrease in the amount of blood passing through the collapsed lung in a unit of time, two other

37 Schlaepfer, K. The Effect of the Ligation of the Pulmonary Artery of One Lung without and with Resection of the Phrenic Nerve, *Arch. Surg.* **13**: 623 (Nov.) 1926. Moore, R. L. Unpublished experiments.

observations stand out in importance (1) the relative decrease in the fraction of blood passing through the blocked lung (as compared with the relative increase in the fraction passing through the functioning lung) which occurred after collapse, and (2) the accompanying decrease in cardiac output. The decrease in the proportion of blood passing through the collapsed lung indicates that local changes within the collapsed lung itself were at least partly responsible for the decrease in its circulation. Of the possible local factors, two are especially deserving of consideration: first, absence of lung motion and second, mechanical obstruction in the capillaries.

The Significance of Immobilization of the Lung—In regard to this factor, it is frequently stated in the literature that the alternate expansion and collapse of the lungs supports the flow of blood through the capillaries. In my experiments, the elastic stretching and recoil of one entire lung was destroyed. What was the effect of this immobilization of the lung? Could it have led to stasis in the vascular bed, which in turn precipitated the circulatory changes that were observed?

In attempting to answer these questions it is at least of some significance to call attention to the fact that total immobilization of a lung does not completely interrupt the pulmonary blood flow. My results show this. Furthermore, if immobilization of a lung did completely interrupt the pulmonary blood flow, total collapse would not follow so quickly in the footsteps of bronchial occlusion. Total collapse of a blocked lung that contains oxygen presupposes absorption of the oxygen by the pulmonary blood stream. This is necessarily so because the oxygen tension within the alveolar spaces is always greater than the oxygen tension of the venous blood. The character of the oxygen absorption curves is still more convincing that complete collapse of a lung which comes on so soon after bronchial occlusion (when an animal is breathing oxygen) is due to absorption of the trapped oxygen by the venous blood. I have noted repeatedly in all of my experiments that for the first few minutes following bronchial occlusion the oxygen absorption of the opposite lung is either unchanged or only slightly increased. Then the curve becomes steeper, and the oxygen absorbed by this lung equals the amount that was being absorbed by both lungs when the control observations were made. The change does not come for several minutes, because it takes this long for the oxygen trapped in the blocked lung to be removed by the blood.

In another study,³⁸ I reproduced tracings showing that partial occlusion of one main bronchus of a dog was followed by a decrease in the amount of oxygen absorbed by the corresponding lung and an

³⁸ Moore (footnote 31, fig 2, p 827)

increase in the amount absorbed by the opposite lung. Under the experimental conditions that existed, the decrease in the oxygen absorption of the partially occluded lung most probably represented a corresponding decrease in the pulmonary blood flow, because the lung was not deflated and the supply of oxygen was not impaired. This observation suggests that limitation, or absence, of lung motion may contribute to the reduced circulation in pulmonary collapse. The fact that the pulmonary circulation is not destroyed when a lung is immobilized, as brought out at the beginning of this paragraph, does not imply that it is not reduced.

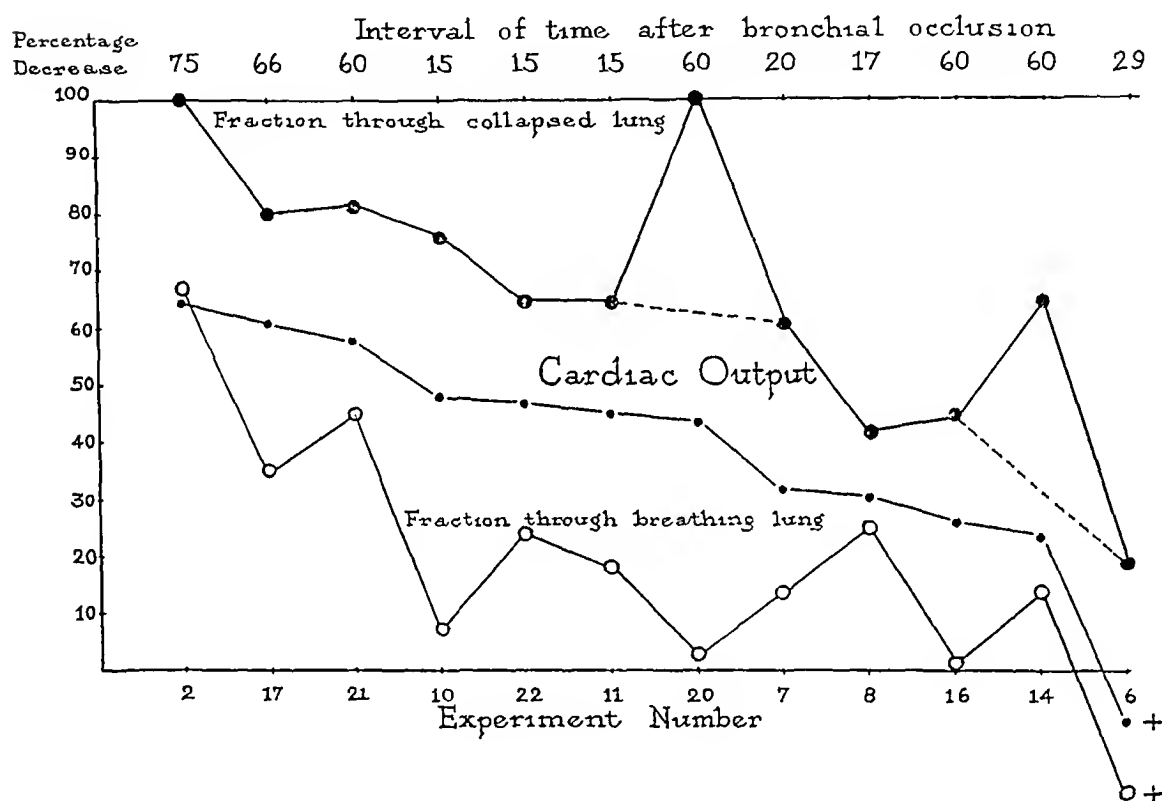


Fig 7—Showing the correlation between changes in cardiac output and fractions of blood passing through the collapsed and breathing lungs. Changes followed occlusion of one main bronchus and absorption of the gases trapped in the alveoli of the corresponding lung. The numbers at the top of the chart represent the intervals of time in minutes which were allowed to elapse between bronchial occlusion and these second estimations of blood flow. The numbers below represent the different experiments. A complete explanation of the chart is given in the text.

The Significance of Obstruction in the Capillary Bed—Most of those writers who have described a diminished pulmonary circulation in a collapsed lung have attributed the decrease to a mechanical obstruction in the capillary bed. They have said that such an obstruction is caused

by the winding and coiling of the vessels which accompany contraction of lung tissue. I have not produced any evidence either for or against this opinion. My microscopic sections show tortuosity of the capillaries, but it would be purely theoretical to conclude from this that the flow of blood is retarded. One cannot estimate function from morphologic appearances.

The Significance of the Decrease in Cardiac Output—If local changes within the lung itself were wholly responsible for the decreased flow of blood through the collapsed lung, one would expect some increase in the circulation through the functioning lung. This occurred, however, only once in my experiments (experiment 6). In eleven instances of twelve the reduced flow through the collapsed lung was accompanied by a decrease not only in the volume of flow through the breathing lung, but also in the total cardiac output. These changes have been correlated in figure 7, and a study of the curves sheds an interesting light on the interpretation of the circulatory adjustments. The changes in cardiac output (expressed in percentage of the initial values) in all experiments are arranged in decreasing order of magnitude, and against each measurement are plotted the simultaneous changes in the fractions of blood passing through the right and left lungs. If experiments 20 and 14 are overlooked, it will be observed that the decrease in circulation through the collapsed lung closely parallels the decrease in cardiac output. It is reasonable to assume that the decrease in cardiac output was precipitated by bronchial occlusion, or one of the consequences of bronchial occlusion (such as immobilization, or collapse of the lung), because the former always followed the latter. This conspicuous decrease in cardiac output is interesting, because it accounts for the rather striking percentage decreases in the fractions of blood passing through both the deflated and the breathing lungs, and, furthermore, because it offers an explanation of the marked differences that were observed in the percentages representing reduced flow in the collapsed lungs. When the left lung was collapsed, the percentage of decrease was greater after the longer intervals, but the time element did not offer a satisfactory explanation for all of the observations. The close parallelism, however, observed between the decrease in circulatory flow through the collapsed lung and the decrease in cardiac output, indicates plainly that the two were related to each other. To what extent, however, the circulation through the collapsed lung was affected by local changes within the lung itself and to what extent by the accompanying decrease in cardiac output, one is not able to say.

The curve that represents the fractions of blood passing through the breathing lungs is more irregular. Theoretically, the irregularity of this

curve could be caused by varying fractions of blood which were shunted through the breathing lung, either by absence of lung motion or obstruction in the vascular bed on the side of collapse

Just why the decrease in cardiac output was moderate in some animals (it increased in one) and large in others is not clear. Nor is it completely clear why the cardiac output decreased at all. It is conceivable that stagnation of blood in the blocked lung was responsible for a part of the decrease. The increase in cardiac output that occurred in experiment

TABLE 7—*The Effect of Occluding One Main Bronchus (Collapsing One Lung) on the Respiratory Rate, Pulse Rate and Expansion of the Opposite Lung*

Experiment Number	Conditions	Respiratory Rate per Minute	Pulse Rate per Minute	Tidal Air		
				Right Lung Cc	Left Lung, Cc	†
8	Control	43	196	33	23	
	Left lung collapsed	50	204	55	0	66.6
7	Control	43	184	39	29	
	Left lung collapsed	44		53	0	35.9
6	Control	80	156	27	24	
	Left lung collapsed	77	154	40	0	32.5
20	Control	13	160	88	17	
	Left lung-collapsed	12	150	115	0	30.6
21	Control	23	108	41	25	
	Left lung collapsed	19	116	61	0	48.8
2	Control	21	148	35	35	
	Left lung collapsed	27	147	60	0	71.4
Average						47.6
10	Control	13	175	52	96	
	Right lung collapsed	12	173	0	162	68.7
11	Control	20	160	57	27	
	Right lung collapsed	40	160	0	64	137.0
22	Control	31	162	41	37	
	Right lung collapsed	48	156	0	53	43.2
14	Control	30	120	32	27	
	Right lung collapsed	47	139	0	44	62.9
16	Control	19	165	55	43	
	Right lung collapsed	26	154	0	70	62.7
17	Control	41	128	36	34	
	Right lung collapsed	50	159	0	57	67.6
Average						73.6

* For the interval of time elapsing between bronchial occlusion and the second observations see table 1

† The figures in this column represent the percentage increase in the tidal air of the "opposite" lung

6, however, makes this interpretation doubtful. It is equally difficult to connect the decrease in cardiac output with intrathoracic pressure changes. If it is assumed that the interpleural partition (mediastinum) in the dog is a freely movable structure and can shift over far enough toward the collapsed lung to equalize the pressure in the two pleural cavities, the amount of negative intrapleural pressure that is developed during inspiration after collapse probably does not differ appreciably from the normal. I believe that this was the situation in all of my experiments. Theoretically (from the standpoint of pressure changes alone), one would not have expected any variation in the filling or output of the heart.

One must exercise caution when applying the results of animal experimentation to clinical conditions. I realize this, but the urge to do research, with some at least, originates in the clinic, and the real pleasure comes when one applies one's ideas to the understanding and treatment of human disease. I undertook this study primarily because I was interested in the physiologic alterations that accompany collapse. Some of those investigators who have preceded me, however, notably Cloetta and Yates, entered into a theoretical discussion of the therapeutic value of the circulatory changes that accompany this condition. Both of these authors expressed the belief that when a lung is put in the position of incomplete deflation its pulmonary circulation is increased, and that this increase in circulation is one of the desired and valuable effects of artificial collapse in clinical conditions. I have not studied the circulation in a partially deflated lung, but my results suggest that in cases of complete deflation (apneumotosis) of a lung the changes in the pulmonary blood circulation would probably have a retarding influence on a diseased process because the blood flow is so strikingly reduced. I am inclined to believe that resting the lung is of greater therapeutic value than the accompanying circulatory changes.

Furthermore, I have produced experimentally a condition that is seen in a surgical ward most frequently as a postoperative complication, and it is now definitely known that many cases of clinical collapse are due to bronchial occlusion. This condition has received much comment in the literature within recent years. It is most often one-sided, and although a one-sided massive collapse is not fatal unless complications develop, the sufferers may be very uncomfortable, and are frequently dyspneic and anoxicemic. That their anoxemia is not due entirely to the passage of fractions of blood through completely unaerated channels is suggested when the administration of oxygen relieves their cyanosis and allows them to breathe easier. When one lung of a dog is rendered functionless during the inhalation of oxygen, the reduction in the saturation of the arterial blood is usually slight. To me, this is an experimental confirmation of the advisability of giving oxygen in cyanotic cases with massive collapse.

SUMMARY

The respiratory movements and oxygen absorption curves of the right and left lungs were recorded separately in fourteen experiments on anesthetized dogs during the inhalation of oxygen. After total occlusion of one primary bronchus and complete collapse of the corresponding lung, similar tracings were taken of the opposite nonobstructed lung. Simultaneous estimations of the oxygen contents of the mixed venous,

arterial and aerated blood specimens were made. The data obtained have been used to calculate cardiac output and fractions of blood passing through the pulmonary system of each lung separately, first under relatively normal conditions and secondly at varying intervals after bronchial occlusion and complete collapse of either lung. It was found that

1. When breathing was free, the amounts of oxygen absorbed by the right and left lungs, respectively, were approximately in the ratio of 3:2.

2. Under similar conditions, the fractions of blood that passed through the right and left lungs were in the same ratio.

3. Total occlusion of one primary bronchus was regularly followed by complete collapse of the corresponding lung.

4. Complete collapse of one lung (either the right or left) was accompanied by a conspicuous decrease in the pulmonary blood circulation on the affected side.

5. The cardiac output and the circulation through the opposite lung decreased to a less extent in eleven of twelve instances.

6. The percentage decrease of blood flow through the collapsed lung varied directly with the decrease in cardiac output.

CONCLUSIONS

The reduced pulmonary blood flow in a lung that has been completely collapsed by bronchial occlusion results in part from local changes within the lung itself and in part from the accompanying decrease in cardiac output. Of the local conditions, absence of lung motion is probably of some importance.

MULTIPLE NEUROFIBROMATOSIS (VON RECKLINGHAUSEN'S DISEASE)

WITH SPECIAL REFERENCE TO MALIGNANT TRANSFORMATION*

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Since the epochal work of von Recklinghausen¹ in 1882, there has been much discussion about the origin and nature of neurofibromatosis. Although the literature contains hundreds of reported cases of multiple neurofibromatosis, the condition is not of frequent occurrence in the experience of any one physician. Malignant transformation of these cutaneous or deep-seated nodules is of unusual interest, especially when one is able to follow a case like the one here reported from the stage of benign neurofibroma to that of spindle cell sarcoma.

REPORT OF CASES

CASE 1—*History*—W F, a white man, aged 28, was admitted in 1927 to the service of Dr. George E. Beilby, Albany Hospital, with the chief complaint of soreness in the right side of his neck and lumps on both sides of his neck. Except for the usual diseases of childhood, his general health had been excellent. In 1920, his tonsils and adenoids were removed. His family history was not remarkable. As regards his present illness, the patient knew he had had a "goiter" for about ten years, but it had been symptomless until July, 1927. At that time, he noticed a "drawing" and an ache in the side of his neck. The swelling itself did not increase in size, possibly it had grown slightly smaller. He had had headaches at night while at work in the railroad yards. There were no tremors of his hands, no sweating or flushing and no loss in weight.

Examination—Physical examination showed a well developed and well nourished young man. There was no motor restlessness. The skin was soft and cool, and showed no flushing. There were numerous soft tumors in the skin, varying in size from about 2 mm to 5 cm in diameter. Most of these cutaneous nodules were sessile, others, pedunculated. Their distribution was irregular. The larger soft masses were on the right shoulder, the upper part of the left arm and the left knee. There was also an irregular brownish pigmentation of the skin. A few pigmented areas measured from 2 to 5 cm in diameter, but most of them resembled freckles (fig. 1).

The skull was symmetrical. There was a slight tenderness over the right mastoid and some fulness on the right side of the pharynx as if a swelling on the outside were pressing inward.

The neck was large and asymmetrical, due to bilateral, large bosselated masses. The mass on the right side was the larger, and extended almost to the

* Submitted for publication, May 2, 1930.

¹ From the Department of Pathology, Albany Medical College, and the Pathological Laboratory of the Albany Hospital.

1 von Recklinghausen, F. Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuomen, Berlin, A. Hirschwald, 1882, pp. 138.

tip of the mastoid process, beyond the midline and down behind the clavicle. The lower pole was not palpable. Pressure on the lower edge caused coughing. The mass on the left side was not so large, its lower pole was also not felt. The trachea was markedly displaced to the left. Many small, indurated discrete nodules were palpable on both sides of the neck. The total tumor mass was firm and somewhat irregular. A loud systolic bruit could be heard over it. There were large dilated veins over the right side of the neck and shoulder.



Fig 1 (case 1) —Patient's back, showing the cutaneous nodules and the patchy pigmentation, appearing mostly as freckles.

The chest was well developed. The right supraclavicular fossa was almost obliterated, the left clavicle being the more prominent. There was a slight increased convexity of the right side of the chest posteriorly. The expansion of the chest was good and symmetrical. The lungs were everywhere resonant, except for a slight impurment at the apex of the right lung. The breath sounds were loud and bronchovesicular, especially at the apex and on the anterior and

posterior part of the right lung. The heart was not remarkable. The abdomen showed no important findings.

There were many bilateral, enlarged, indurated nodules in the cervical, axillary, epitrochlear and inguinal regions.

Roentgen examination by Dr. William P. Howard showed a large mass in the mediastinum extending above the heart into the root of the neck, which suggested a retrosternal thyroid gland, measuring 14 cm. in its greatest transverse diameter. The trachea was displaced toward the left and apparently compressed (fig. 2).



Fig. 2 (case 1).—Roentgenogram showing a very large mediastinal mass protruding into the right pleural cavity and extending from above the heart into the root of the neck. The trachea is displaced toward the left.

The urinalysis was of no interest. The Wassermann test of the blood was negative.

Operation.—At operation, an exploratory thyroid incision was made. The tumor mass extended behind the manubrium sterni and was soft. As total removal would necessitate resection of ribs, only a piece of the tumor was removed for diagnosis. The pathologic diagnosis by Dr. Victor C. Jacobsen was edematous fibroma. The patient was discharged improved.

Second Admission.—The patient was readmitted to the hospital in January, 1928, for further observation. Except for the operative scar, the physical signs were essentially the same as those previously described.

In July, 1928, the right side of the neck became enormously swollen. It was incised, and some degenerating necrotic material was allowed to drain. Roentgen examination at that time showed a large mass projecting from the root of the neck into the right side of the chest, displacing the trachea toward the left side. This area was approximately 13 by 12 cm.



Fig. 3 (case 1) — Appearance of patient on his final admission. Note the large, irregular, almost pendulous tumor mass in the neck, the many small cutaneous fibromas, sessile and pedunculated, and the patches of pigmentation.

Third Admission—The patient was admitted to the hospital for the third time in September, 1928. The chief complaints at this time were pain and ache in the left side of his head and in his left shoulder. Examination showed numerous sessile or pedunculated tumor masses in the skin along the course of different nerves varying in size from 2 mm to 5 cm. In the neck, there were large, asymmetrical bilateral masses, larger on the right which extended to the right

mastoid process (fig 3) The lower pole extended behind the sternum Pressure over this region caused coughing The lower pole on the left side was also not palpable The trachea was displaced to the left The left clavicle appeared slightly prominent Many other small discrete skin nodules were palpable

At operation, the tumor masses were found to be markedly vascular That portion projecting above the sternum was myxomatous and very friable Anteriorly, it crossed the midline to the left, evidently invading muscle Bleeding was controlled by sutures Two drains were inserted in the cavity formed by the removal of the part of the tumor mass The pathologist's diagnosis this time was spindle cell sarcoma

After leaving the hospital, the patient continued to grow worse, and he died a month later Autopsy could not be obtained

Microscopic Examination of Tissue Removed in 1927—The specimen was fixed in Zenker's solution Paraffin sections were stained with hematoxylin and eosin, van Gieson's trinitrophenol fuchsin, Mallory's phosphotungstic acid

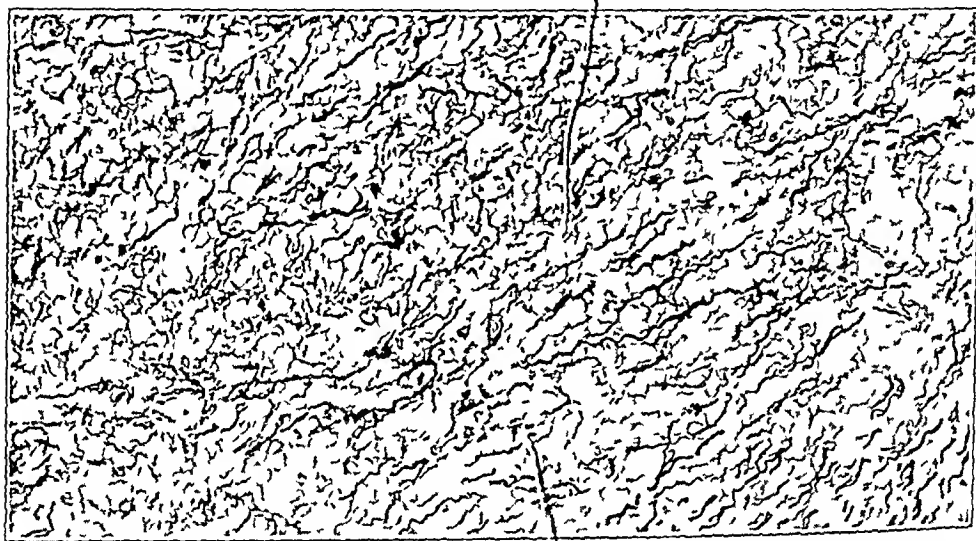


Fig 4 (case 1)—Photomicrograph of a section of the large cervical tumor The numerous reticulum fibrillae are in intimate association with the tumor cells Foot and Menard's silver stain, lightly counterstained with Harris' hematoxylin, $\times 197$

hematoxylin, Weigert's resorcin fuchsin, Foot and Menard's ammonium silver and Laidlaw's lithium silver

All the sections were very poor in cells, which were widely separated from one another by edematous stroma composed of little reticulum but of numerous thin, wavy strands of collagen These cells were either spindle-celled or stellate in shape and small The nucleus was generally ovoid, more or less vesicular, and had a minute insignificant nucleolus There were no mitotic figures No nerve trunks were demonstrable in the sections of the tumor proper

Microscopic Examination of Tissue Removed in 1928—These sections were very cellular In fact, the cells were so densely packed together that hardly any collagen fibrils were demonstrable over wide areas But when the silver stains were used, in intimate association with each tumor cell were delicate reticulum fibrillae which formed a fine intricate network (fig 4) After the Laidlaw stain, the nuclei were silver-negative, so that only the fine dense meshwork

was seen. With the Mallory stain fibroglia could be demonstrated streaming from the tumor cell. No elastic fibrils were present. Mitotic figures were very abundant. The tumor cells had invaded the striated muscles of the neck. The microscopic picture was now that of a rather anaplastic type of fibroblast, rapidly growing and infiltrating adjacent structures. The tumor cells were large, with conspicuous round or oval nuclei (fig 5). Blood vessels of the capillary type were quite numerous. These tumor cells were often grouped more densely around these capillaries in a perithelial manner and had even invaded some vessels.

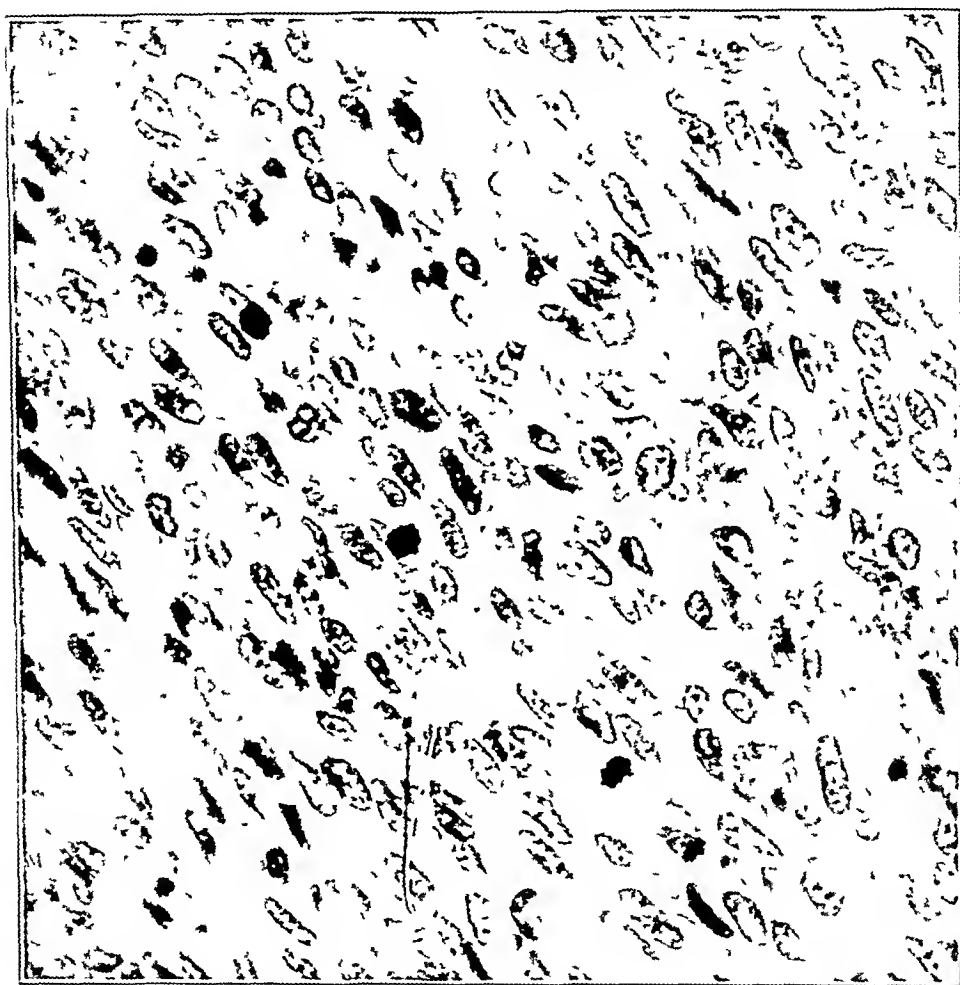


Fig 5 (case 1)—Photomicrograph of a cellular area from the large cervical tumor. Note the three mitotic figures. Hematoxylin and eosin stain, $\times 248$.

This invasion of blood vessels would indicate although no necropsy could be obtained that the patient probably died from internal metastasis as judged from the progressive cachexia just before his death. In some sections, there were large areas of intense edema with cystic spaces containing coagulated fluid and strands of fibrin. Small hemorrhages were present here and there.

Fortunately, pieces of adjacent muscle tissues were also removed at the time of the last operation. In addition to the invasion of the muscle by the sarcoma as observed at operation some interesting and important information was obtained on microscopic study. Serial sections were made of all the muscle blocks. Some

of the small nerves in the perimysium showed a more or less marked concentric proliferation of the perineurium (fig 6), in others, the proliferating perineurium appeared like a crescent around the nerve.

As regards the muscle fibers themselves, most of them appeared normal. Scattered here and there were many typical muscle spindles. In addition, small collections of lymphocytes were present among the muscle fibers.

In some areas adjacent to the sarcoma, the perivascular tissues and even the walls of the arterioles and venules were infiltrated with polymorphonuclear leukocytes without, however, any thrombosis. In other areas, there was a dense perivascular lymphocytic infiltration. In the cystic portions of the tumor proper, a few of the venules showed hyaline mural thrombi.

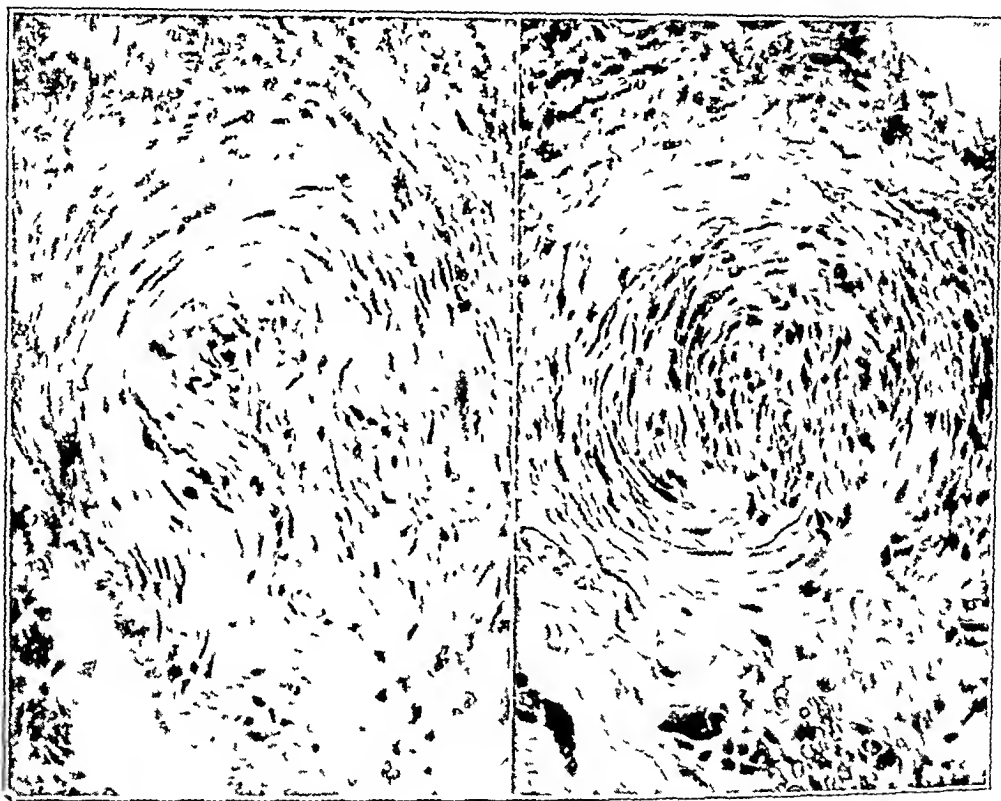


Fig 6 (case 1)—Photomicrograph of two different small nerve bundles, showing the concentric proliferation of the perineurium. Mallory's eosin-methylene blue stain, $\times 306$.

CASE 2—History—F. L., a white man, aged 68, was admitted in 1929 to the service of Dr. Thomas Ordway, Albany Hospital, because of a troublesome, productive cough of two weeks' duration. The day prior to admission, he felt chilly and had a severe headache. He said that he had not been sick before. Several years ago, he fractured his right shoulder and several ribs, ever since then, the right side had hurt him whenever he coughed. A hernia had been present since childhood. He had been having nocturia (once) for the last several years. When he was 10 years old, small lumps began to develop in his skin. They had progressed in size and number up to the present time, but had never caused any inconvenience. His family history, including that of his five children, was entirely uninteresting, except for one important fact: one sister had small lumps over her body similar to his own condition.

Examination—Physical examination of the nose, throat and chest showed nothing remarkable. No masses were felt in the abdomen. There was a large indirect inguinal hernia. Covering the entire trunk, so thickly scattered that it was impossible to find an area large enough to lay a stethoscope flat, there were soft nodules varying in size from that of a pinhead to that of a walnut. The larger nodules were pedunculated, soft and flabby, not tender, and covered with



Fig 7 (case 2)—Patient's back, showing the thickly set distribution of the mollusca fibrosa, varying in size from that of a pinhead to that of a walnut

apparently normal skin (fig 7). Some of these nodules were located deeply in the subcutis. They were present in great numbers on the various surfaces of all four extremities and on the neck, face, scalp and even the eyelids. They were most numerous on the trunk.

The urine was alkaline, showed a trace of albumin, no sugar and contained much cellular debris. The Wassermann and Kahn tests of the blood were negative. Chemical examination of the blood gave a nonprotein nitrogen of

36.6 mg and a sugar of 90 mg per hundred cubic centimeters. The hemoglobin was 90 per cent. The systolic blood pressure was 115 mm, the diastolic 80 mm. None of the cutaneous nodules was excised for microscopic examination.

COMMENT

The mesodermal origin of multiple neurofibromas from the epineurium, perineurium and endoneurium of the nerve bundles is now generally accepted. However, Verocay² expressed the belief that they are ectodermal, arising from the cells of the sheath of Schwann. The adherents of the latter theory have given various names to these tumor formations—neurinoma (Verocay), schwannoma (modern French writers) and glioma (Bertrand and Charrier³ and others). Whether the cells of the sheath of Schwann are specialized glia cells or not is still a much disputed point. According to Penfield,⁴ multiple neurofibromatosis is a generalized fibrous connective tissue reaction showing both nerve fibers and connective tissue elements in the tumors. He classified the neurinoma, solitary neurofibroma, gliome périphérique and acoustic neuroma under the general heading of perineurial fibroblastoma. For a complete discussion of the subject, the reader is referred to the classic monographs of von Recklinghausen, Thomson,⁵ Adrian,⁶ Verocay and Herxheimer and Roth.⁷

Isolated primary fibrosarcomas and spindle cell sarcomas of the different nerves without an associated von Recklinghausen's disease have been reported by Hume,⁸ Kriege,⁹ Peet,¹⁰ McArthur,¹¹ Villegas

2 Verocay, J. Zur Kenntnis der "Neurofibrome," Beitr z path Anat u z allg Path **48** 1, 1910.

3 Bertrand, I., and Charrier, J. Cystic Glioma of the Ulnar Nerve, Rev neurol **38** 1345, 1922.

4 Penfield, W. The Encapsulated Tumors of the Nervous System, Meningeal Fibroblastomata, Perineurial Fibroblastomata and Neurofibromata of von Recklinghausen, Surg Gynec Obst **45** 178, 1927.

5 Thomson, A. On Neuroma and Neuro-Fibromatosis, Edinburgh, Turnbull & Spears, 1900, pp 168.

6 Adrian, C. Ueber Neurofibromatose und ihre Komplikationen, Beitr z klin Chir **31** 1, 1901.

7 Herxheimer, G., and Roth, W. Zum Studium der Recklinghausen'schen Neurofibromatose, Beitr z path Anat u z allg Path **58** 319, 1914.

8 Hume, G. H. A Case of Sarcoma of the Internal Popliteal Nerve, Lancet **2** 344, 1886, Cases of Tumor of Nerve Trunks, Illustrating the Results of Excision of the Tumor Along with the Affected Portion of Nerve, Lancet **2** 654, 1891.

9 Kriege, H. Ueber das Verhalten der Nervenfasern in den multiplen Fibromen der Haut und in den Neuomen, Virchows Arch f path Anat **108** 466, 1887.

10 Peet, M. M. Spindle Cell Sarcoma Arising in a Cavernous Lymph- and Hem-angioma of the Musculospiral Nerve, J Michigan M Soc **16** 320, 1917.

11 McArthur, L. L. Sarcoma of the Posterior Tibial Nerve. Excision, Removal of Metastatic Foci in Retroperitoneal Lymph Glands Three Months Later, S Clin North America **4** 131, 1920.

and Rojas,¹² McGuire and Burden¹³ and many others. The nerves involved in the foregoing cases were the sciatic, median, musculospiral, internal popliteal and posterior tibial. In Meyer's case,¹⁴ the fibrosarcoma was of the hour-glass type with intradural and extradural portions extending from the sixth cervical to the first dorsal segments. Kredel and Beneke¹⁵ described a spindle cell sarcoma, involving both the median and ulnar nerves, in an infant 2 months old. In Buford and Davis' case,¹⁶ the tumor of the sciatic nerve at the first removal was a typical fibroma which at a later date had become sarcomatous. In 1900, Thomson collected twelve cases of authenticated primary sarcomas of nerves, 50 per cent of these occurring in the great sciatic nerve. Allenbach,¹⁷ in 1921, collected twenty-four cases of sarcomas of the sciatic nerve, but added that in most only the gross description was given without microscopic observations. Garre¹⁸ differentiated between the primary sarcoma of nerves not associated with von Recklinghausen's disease and the secondary sarcoma of nerves in which the latter is due to a sarcomatous transformation of one of the preexisting neurofibromas. The primary form is similar to other types of sarcomas, being characterized by great malignancy. The growth reaches considerable size in a few months, invades the surrounding tissue and leads not infrequently without local or regional recurrence to internal metastasis. The patient succumbs to the generalized sarcomatosis in a short time. In great contrast to the foregoing form, in the secondary form one of the neurofibromas undergoes malignant transformation frequently following trauma or often without known cause, and begins to grow rapidly. However, this growing tumor remains enclosed in its connective tissue capsule for a long time. Operative intervention appears to have a stimulating effect. Recurrence is local or in nearby nerves. Internal metastasis occurs late.

In all those cases in which a sarcoma was found associated with multiple neurofibromas at the time of the first examination, the authors

12 Villegas, R. R., and Rojas, P. Consideraciones sobre los tumores primitivos de los nervios. A proposito de un fibrosarcoma de la vaina del ciatico, *Semana med* **27** 675, 1920.

13 McGuire, E. R., and Burden, J. F. Unusual Case of Sarcoma of the Median Nerve, *Surg. Gynec. Obst.* **35** 453, 1922.

14 Meyer, E. Zur Kenntnis der Rueckenmarkstumoren, *Deutsche Ztschr. f. Nervenhe.* **22** 232, 1902.

15 Kredel, L., and Beneke, R. Ueber Ganglioneurome und andere Geschwuelste des peripheren Nervensystems, *Deutsche Ztschr. f. Chir.* **67** 239, 1902.

16 Buford, C. G., and Davis, T. A. Sarcoma of the Sciatic Nerve, *Surg. Gynec. Obst.* **20** 495, 1915.

17 Allenbach, E. Le sarcome du nerf sciatique, *Rev. de chir.* **59** 134, 1912.

18 Garre, C. Ueber sekundaer maligne Neurome, *Beitr. z. klin. Chir.* **9** 465, 1892.

concluded from the symptomatology that one of these neurofibromas had undergone a sarcomatous change. According to Garré, there is a striking tendency to sarcomatous transformation in multiple neurofibromatosis, for in at least 12 per cent of all cases this sarcomatous change takes place from a benign neurofibroma. Garré calculated this percentage on the basis of seventeen collected cases. From table 1, it is seen that up to 1927 there were reported fifty-nine cases of sarcomatous transformation in von Recklinghausen's disease. Using the 1927 figures of Fischer,¹⁹ when he collected reports of 466 cases of von Recklinghausen's disease, one obtains an incidence of malignant changes of about 13 per cent which is in agreement with Garré. These neurosarcomas have been observed most frequently in the deeper nerve trunks. Ewing²⁰ stated that the serious nature of these deeper tumors is very imperfectly realized by most surgeons, so that the number of victims of this disease is much larger than is generally believed. He added that the primary attack on these tumors must be undertaken with great caution. Stromeyer²¹ performed a disarticulation for a sarcoma of the median nerve which had invaded the adjacent structures. In de Morgan and Coupland's case,²² a plexiform neurofibroma of the musculospiral nerve, associated with elephantiasis of the skin of the forearm, became sarcomatous. The musculocutaneous nerve was involved by the sarcomatous growth in Vangehr's case.²³ Pomorski²⁴ described a large intrathoracic tumor which compressed the ascending vena cava, causing hydrops, ascites and anasarca. The clavicular tumor in Modrzejewski's case²⁵ suddenly began to grow rapidly, reaching the size of a man's head, and became very painful. Westphalen²⁶ reported a case of multiple fibromas of the skin, nerves and ganglions, one of which in the fifth cervical nerve underwent a sarcomatous change.

19 Fischer, G. A. Recklinghausensche Krankheit und Muttermaeler, *Dermat Wchnschr* **84** 89, 1927.

20 Ewing, J. Neoplastic Diseases, ed 2, Philadelphia, W. B. Saunders Company, 1922, p 152.

21 Stromeyer. Handbuch der Chirurgie, 1844, vol 1, p 413, cited by Garré (footnote 18).

22 De Morgan, C., and Coupland. Case of Multiple Neuroma of the Forearm, *Tr Path Soc London* **26** 2, 1875.

23 Vangehr, A. Inaug-Diss., Munich, 1881, cited by Garré (footnote 18).

24 Pomorski, J. Ein Fall von Rankenneurom der Interkostalnerven mit Fibroma molluscum und Neurofibromen, *Virchows Arch f path Anat* **111** 60, 1888, Inaug-Diss., Greifswald, July 30, 1887.

25 Modrzejewski, E. Multiple angeborene Fibromata mollusca (sogenannte Neurofibrome von Recklinghausen's), *Berl klin Wchnschr* **19** 627, 1882.

26 Westphalen, H. Multiple Fibrome der Haut, der Nerven und Ganglien mit Uebergang in Sarcom, *Virchows Arch f path Anat* **114** 29, 1888.

In then cases of multiple neurofibromatosis Campana²⁷ described a sarcomatosis of the skin, Sorger²⁸ a sarcoma of the axilla, von Gernet²⁹ a sarcomatous transformation of a massive plexiform fibroma of the shoulder and upper part of the arm, Heydweiller³⁰ a fibrosarcoma of the right popliteal space, Feindel³¹ a sarcome globocellulaire of the leg, and Gluge³² a sarcoma in the pelvis, the size of a child's head. Rolleston³³ described a sarcomatous growth involving the brachial plexus which occupied the anterior mediastinum on the left side, obliterated the internal jugular vein at its termination invaded the structures of the neck and left lung and eroded the bodies of the fifth, sixth and seventh cervical vertebrae. The abdominal sympathetics around the aorta showed nodular fibromatous thickenings. In Cimmino's case,³⁴ a large sarcoma in the sacral region was associated with about 450 fibromatous tumors of the skin. Jeanselme and Orrillard³⁵ reported a case of fibrosarcoma of the saphenous nerve with elephantiasis molle congenita of the overlying skin. Adrian³⁶ found at necropsy a fibrosarcoma of the duodenum which was associated with multiple fibromas of the skin and internal viscera and a neuromyxoma in the supraclavicular fossa about the size of a child's fist. In MacKenzie's case³⁷ in addition to the multiple soft tumors in the skin a goose egg-sized sarcoma of the sciatic nerve was observed. In Kohtz's case,³⁸ besides the numerous nodules on the anterior and

27 Campana. Ueber Sarkomatose der Haut. XII Kongress der ital Aerzte zu Pavia, Sept 19-25, 1887, Sektion fuer Syphilis u Hautkrankheiten, Monatsh f prakt Dermat **7** 30, 1888

28 Sorger, J F. Beitrag zur Lehre von den multiplen Neurofibromen, Inaug-Diss, Erlangen, Dec 22, 1890, p 31

29 von Gernet, R. Das plexiforme Fibrom der nerven und der Haut. Ein Beitrag zur Geschwulstlehre, Inaug-Diss, Dorpat, April 4, 1892, p 23

30 Heydweiller, E. Ein Beitrag zur Casuistik der multiple Fibrombildungen der Haut (Mollusca fibrosa), Inaug-Diss, Erlangen, Dec 30, 1887, p 28

31 Feindel, E. Sur quatre cas de neurofibromatose generalisee, These de Paris, 1896, no 104, p 76

32 Gluge, G. Abhandlungen zur Physiologie und Pathologie, 1841, p 140, cited by Garre (footnote 18)

33 Rolleston, H D. A Case of Recklinghausen's Disease Complicated with a Sarcomatous Growth Involving the Brachial Plexus, Lancet **2** 271, 1899

34 Cimmino, R. Su di un caso di fibromi multipli cutanei con metamorfosi sarcomatosa, Gior ital d mal ven **26** 28, 1891

35 Jeanselme, E, and Orrillard. Contribution a l'etude des malformations congenitales de la peau et de l'hypoderme, Rev de chir **14** 50, 1894

36 Adrian, C. Ueber einen bemerkenswerthen Fall von Neurofibromatosis, Wien klin Wchnschr **15** 813, 1902

37 MacKenzie, K A J. Resection of the Sciatic Nerve, Ann Surg **50** 295, 1909

38 Kohtz. Ein Fall von multiplen Fibromen der Haut, Inaug-Diss, Koenigsberg, March 10, 1893, p 28

cardiac surfaces of the stomach and several subserous nodules in the small intestines and the mesentery, there was a sarcomatous tumor of the duodenum. Shouldice³⁹ reported a case of multiple peripheral fibromas in which operation disclosed dozens of small tumors about the size of millet seeds all over the stomach and a fibromyxosarcoma on the greater curvature of the stomach. Wright⁴⁰ noted a case of familial neurofibromatosis in which a sarcomatous change took place in one of these tumors in the thigh. Feriz's case⁴¹ showed mollusum fibrosum, elephantiasis neuromatosa of the skin of the right leg, and a large fibrosarcoma of the lateral aspect of the thigh. In a case of multiple peripheral neurofibromatosis, Hartman⁴² described a large fibromyxosarcoma of the stomach which he believed arose presumably in a neurofibroma of the gastric wall. In one of Gray's cases,⁴³ necropsy showed a spindle cell sarcoma of the mediastinum.

It has been clinically observed that partial removal or any operative trauma of a neurofibroma may activate the tumor into a sarcoma. In Arnozan's first case,⁴⁴ a plexiform neurofibroma of the right side of the neck became sarcomatous after the operation and gradually increased in size during an interval of fifteen years, measuring 40 by 10 by 10 cm and weighing 1,850 Gm. The pedunculous tumor masses finally became gangrenous and the patient died from septicemia. Goldmann⁴⁵ removed a fibromyxoma of the tenth intercostal nerve extending from the level of the eighth dorsal to that of the first lumbar vertebra. A year later, the patient returned with an equally large tumor, recurrent in the operative scar. After the second operation, the second recurrence grew rapidly, reaching the size of a child's head within two months. Microscopic examination of the recurrent tumors showed a spindle cell sarcoma. There was no internal metastasis.

39 Shouldice, E. Multiple Fibromata—A Case With One Fibroma Enlarging Into the Stomach, *Canad M A J* **15** 66, 1925.

40 Wright, A., quoted by Shouldice (footnote 39).

41 Feriz, H. Neurofibromatosis und Sarkom, *Deutsche Ztschr f Chir* **192** 372, 1925.

42 Hartman, H. Fibro-Myxo-Sarcoma of the Stomach in a Case of Neurofibromatosis (von Recklinghausen's Disease), *Surg Gynec Obst* **44** 308, 1927.

43 Gray, S. H. The Histogenesis of von Recklinghausen's Disease, *Arch Neurol & Psychiat* **22** 91 (July) 1929.

44 Arnozan, X. Névrome plexiforme, *J de med de Bordeaux* **15** 72, 1885, *Trois cas de nevrome plexiforme dans le recueil d'observations de dermatologie, Bordeaux, 1892*. Meslet. Contribution a l'étude des nevromes plexiformes, *Inaug Diss, Bordeaux, 1892*, no. 6.

45 Goldmann, E. E. Beitrag zu der Lehre von den Neuromen *Beitr z klin Chir* **10** 13, 1893.

at necropsy In Delore and Bonne's case,⁴⁶ a cellular neurofibroma developed on the exact spot where a violent blow had been received three years previously There were two operations inside of three months, the second being for recurrence Ten months later, there was a second recurrence Harbitz⁴⁷ reported fourteen cases of von Recklinghausen's disease, in two of which there occurred a sarcomatous transformation in a preexisting fibromatous nodule In one of these cases, a fibroma of a thigh nerve underwent sarcomatous changes after ten repeated attempts at extirpation in the course of eighteen years In the second case, a plexiform neurofibroma of the left sciatic nerve after repeated removals and recurrences finally became sarcomatous In my first case, an edematous fibroma of the lower cervical and upper mediastinal regions at the second operation about one year later had already become a very cellular spindle cell sarcoma

Furthermore, even after complete extirpation of a sarcomatous tumor, another neurofibroma in a different location may undergo sarcomatous transformation In von Winiwarter's case,⁴⁸ it is interesting to note that the operative removal of even a benign neurofibroma in the left scapular region was soon followed by a sarcomatous transformation of the preexisting neurofibroma of the left radial nerve Finotti⁴⁹ reported a case of fibroma durum epineuricum of the great sciatic nerve, when the patient was seen again about eleven months after the operation, there was no recurrence at the site of the operation, but on the posterior aspect of the leg close to the lower part of the popliteal space, a fibrosarcomatous nodule was removed Hartmann⁵⁰ excised a fibrosarcoma of the right axilla In the course of a year, a tumor the size of a goose egg appeared in the right groin, which after operative removal was found to be a fibroma in the lower part of the tumor, calcified in the central portions, and a spindle cell sarcoma in the upper part In Habermann's case,⁵¹ about a year after the removal of a fibrosarcoma of the right sciatic nerve, another fibrosarcoma developed in the right ulnar nerve which was removed and the nerve sutured

46 Delore, X., and Bonne, C. Neuro-fibromatose et nevrome plexiforme, *Gaz hebdomadaire de medecine et de chirurgie* **45** 145, 1898 Delore Neuro-fibromatose cutanee avec anthrome profond du bras droit, *Gaz de l'hopital* **69** 514, 1896

47 Harbitz F. Multiple Neurofibromatosis (von Recklinghausen's Disease), *Archiv Internae Medecine* **3** 32 (Feb) 1909

48 von Winiwarter, A. Plexiformes Fibro-neurom der Armnerven mit circumscribter Hauthypertrophie und Sarcomentwicklung, *Archiv für klinische Chirurgie* **19** 595, 1876

49 Finotti, E. Beiträge zur Chirurgie und pathologischen Anatomie der peripherischen Nerven, *Virchows Archiv für pathologische Anatomie* **143** 133, 1896

50 Hartmann H. Zur Kenntnis der sekundären malignen Neurome, *Beiträge zur klinischen Chirurgie* **17** 177, 1896

51 Habermann. Beitrag zur Kenntnis der sekundären malignen Neurome, *München medizinische Wochenschrift* **45** 713-716, 752-754, 1898

together. About nine months later, painful nodules developed in the left occipital region, which on removal showed beginning fibrosarcoma. There were no local recurrences after each of the three operations. In Thomson's case, a rapidly growing tumor of the right median nerve was removed, which proved to be a spindle cell sarcoma at one point in the sections. The sarcoma recurred twice, each followed by an operation, the last being a shoulder amputation. It recurred for the third time in the vicinity of the scar. Necropsy revealed the unexpected finding of a spindle cell sarcoma of the left lumbar plexus, about the size of a child's head, involving the psoas muscle and the adjacent bodies of the vertebrae. In Heixheimer and Roth's first case, there were multiple neurofibromas of the peripheral nerves, one of which in the anterior thigh became sarcomatous. Soon after its operative removal, a nodule in the neck began to enlarge rapidly, causing marked compression of the trachea. Necropsy showed that the sarcomatous tumor in the neck had extended into the left thoracic cavity, where it was adherent to the apex of the lung. There was also a metastatic nodule in the right lung.

Recurrences may be frequent and are generally local or regional after operative measures. Such recurrences may be repeated several times before distant metastasis takes place. In fact, the absence of metastasis is remarkable in the reported cases in which there were repeated operations for recurrences. Hitchcock⁵² removed a sarcoma of the ulnar nerve which recurred. Amputation at the shoulder joint was performed, which was followed by a second recurrence in the shoulder. There was no necropsy. In Girard's first case,⁵³ three operations were performed for the original tumor and the two recurrences. The patient was still living at the last report. Volkmann,⁵⁴ Virchow⁵⁵ and Blasius⁵⁶ separately reported the progress notes of several interesting cases. In the case of Volkmann and Blasius, the patient had three operations for a tumor of the median nerve during the course of eight years, each time there was a recurrence. At necropsy, there was no metastasis. In the case of Virchow and Blasius the patient had six operations for the original tumor, with five recurrences. There was no

52 Hitchcock, A. Some Remarks on Neuroma with a Brief Account of Three Cases of Anomalous Cutaneous Tumors in One Family. *Am J M Sc* **43** 320, 1862.

53 Girard. Transformation de molluscums et de naevi en sarcome et en épithéliome, *Dauphine med* **22** 1, 1898.

54 Volkmann, R. Ueber ein faustgrosses ulceriertes Neurom im Handteller. *Virchows Arch f path Anat* **12** 27, 1857.

55 Virchow, R. Ueber einen Fall von vielfachen Neuromen (sogenannten Faser-Kern-geschwuelsten) mit ausgezeichneter localer Recidiv-faehigkeit. *Virchows Arch f path Anat* **12** 114, 1857.

56 Blasius, E. Ueber rueckfaellige Neurome, *Arch f klin Chir* **2** 188, 1862. Ueber rueckfaellige Neurome, *ibid* **6** 775, 1865.

necropsy In the case of Blasius, the patient had three operations with two recurrences The patient was said to be entirely well about a year later Von Bergmann⁵⁷ presented a patient before the Berlin Surgical Society, on whom operation for a spindle cell sarcoma of the left axillary and scapular regions was followed by a recurrence and rapid growth As mentioned previously, in the cases of Arnozan and of Goldmann, a plexiform neurofibroma and a fibromyxoma respectively recurred as sarcomas after operative intervention At necropsy, there was no internal metastasis in either of these cases Thilow⁵⁸ reported two cases, in one of which there were recurrences nearby In Tichoff and Timofejeff's case,⁵⁹ three operations were performed for a spindle cell sarcoma of the popliteal space with two recurrences No metastasis was found at necropsy Scheven⁶⁰ described a spindle cell sarcoma of the median nerve, four operations were performed because of recurrences Necropsy did not reveal any internal metastasis Vallas⁶¹ presented a patient with generalized neurofibromatosis who showed a recurrence in the scar, and who had already been operated on five or six times for a large tumor of the eighth intercostal nerve

From table 1 it is seen that metastasis is relatively infrequent when a benign neurofibroma becomes sarcomatous There were fourteen metastatic cases among a total of sixty-five or 22 per cent Metastasis occurred eleven times in the lung, four times in the pleura, twice in the diaphragm and the liver and once each in the humerus, pubic bone and paravertebral lymph node It is to be noted, however, that once malignancy has supervened, the prognosis is generally bad The patients succumb to the progressive cachexia resulting from the many recurrences, metastasis and repeated operations Busch⁶² performed an amputation of the leg for a sarcoma of the peroneal nerve with recurrence and invasion of the bone Necropsy showed numerous sarco-

57 von Bergmann Presentation of Case, Verhandl d Freie Vereinigung der Chirurgen Berlins, Sitzung Nov 18, 1889, koeniglichen Klinikum, Berl klin Wchnschr **26** 1133, 1889

58 Thilow, C Beitrage zur Casuistik des Fibroma molluscum multiplex, Inaug-Diss, Berlin, Oct 25, 1889 The same case was presented by Schlang before the Freie Vereinigung der Chirurgen Berlins, Jan 14, 1889, koeniglichen Klinikum, Berl klin Wchnschr **26** 122, 1889

59 Tichoff and Timofejeff Multiple Neurofibroma with Fibroma Molluscum Multiplex, Chir Ann (Russian), 1894, p 719, abstr, Jahr u d Leistung in d ges Med, XXIX Jahrgang, Bericht fur das Jahr 1894, Berlin, A Hirschwald, 1895, vol 2

60 Scheven, O Zur Kenntnis der sekundaer malignen Neurome, Beitr z klin Chir **17** 157, 1896

61 Vallas Neuro-fibromatose generalisee, Soc de Chir de Lyon June 29, 1899, Lyon med **92** 132, 1899

62 Busch Handbuch der allgemeinen und speciellen Chirurgie Erlangen, Pitha & Billroth, 1865, vol 2, p 239, cited by Garre (footnote 18)

matous nodules along the intercostal nerves and lungs. In Genersich's case,⁶³ necropsy showed that the right sciatic sarcoma had produced metastatic nodules in both lungs, in several of which the arteries were occluded with fibrin and spindle cells. In two of the cases reported by Rose,⁶⁴ a myxosarcoma of the sciatic nerve and a retroperitoneal sarcoma of the cranial nerve metastasized to the lung and to a paravertebral lymph node, respectively. Hume observed in a case of molluscum fibrosum a sarcoma of the great sciatic nerve with metastasis to the pleura, left lung, liver and left humerus. Westphalen⁶⁵ reported an unusual case of spindle cell sarcoma of the sciatic nerve located in the popliteal space, which in spite of the disarticulation of the hip joint at the very first operation had already metastasized to the lung and pleura. Poncet⁶⁶ performed an amputation for sarcoma of the thigh but the patient succumbed to a generalized sarcomatosis. Adrian, in 1901, reported an interesting case of fibromyxosarcoma growing in the region of a meningocele, with metastasis to the diaphragm and lung. In a case of multiple neurofibromatosis, Potter and McWhorter⁶⁷ recently described a spindle cell sarcoma over the occiput which perforated the skull and formed a thick plaque over the dura, and which also metastasized to the visceral pleura and lung.

Primary multiple sarcomas arising in two or more neurofibromas in von Recklinghausen's disease appear to be a rare phenomenon. In von Recklinghausen's own case, two of the largest nodules on the jejunum were sarcomatous. Seitz' case⁶⁸ showed multiple tumors of the skin and nerves, the largest of which was in the left peroneal nerve and was about the size of a fist. There was a total of twenty-two nodular tumors of the various nerves of the body. Seitz believed his case to be one of multiple round and spindle cell sarcomas. In Arnozan's second case, a congenital plexiform neurofibroma of the right side of the neck became a sarcome fasciculé within six months following a blow, and recurred after removal. Another small pedunculated fibroma on the patient's back on removal showed early sarcomatous changes. This

63 Genersich, A. Multiple Neurome, Virchows Arch f path Anat **49** 15, 1870

64 Rose, E. Ueber die Exstirpation gutartiger Bauchgewächse (Die Laparektomie), Ztschr f Chir **19** 24, 1884, Ein Neurom der Erb'schen Plexuswurzeln, ibid **24** 392, 1886

65 Westphalen, H. Multiple Fibrome der Haut und der Nerven mit Uebergang in Sarcom und mit Metastasenbildung, Virchows Arch f path Anat **110** 29, 1887

66 Poncet, A. Discussion in Tr Société nationale de médecine, March 29, 1897, Lyon méd **84** 520, 1897

67 Potter, P. C., and McWhorter, J. E. Von Recklinghausen's Disease with Sarcomatous Degeneration of a Deep Fibroma, Ann Surg **90** 397, 1929

68 Seitz, J. Multiple Fibrosarkome der Nerven und Perichondritis laryngea, Virchows Arch f path Anat **52** 114, 1871

TABLE 1—*Sarcomatous Transformation in Neurofibromatosis*

No	Author	Sex	Age	Location of Sarcoma	Operation	Local Recurrence	Internal Metastasis	Result
1	Gluge, 1841	M	34	Pelvis				?
2	Stromeyer, 1844	M	19	Median nerve	Yes			
3	Volkmann, 1857	F	19	Median nerve	Yes, 3	Yes, 3	None	Died
	Blasius, 1862							
4	Virchow, 1857	M	56	Wrist	Yes, 6	Yes, 5		Died
	Blasius, 1862							
5	Blasius, 1862	M	53	Arm	Yes, 3	Yes, 2		Living
6	Hitchcock, 1862	M	40	Ulnar nerve	Yes, 2	Yes, 2	? (no necropsy)	Died
7	Busch, 1865			Peroneal nerve	Yes, 2	Yes, 2	Lung, pleura	Died
8	Genersieh, 1870	M	22	Sciatic nerve			Lung	Died
9	Seitz, 1871	M	48	Peroneal nerve	No		No	Died
10	De Morgan and Coupland, 1875	F	15	Musculospiral nerve	Yes	?		Living
11	Von Winiwarter, 1876	M	36	Radial nerve	Yes		Lung	Died
12	Vangehr, 1881	F	42	Musculocutaneous nerve	Yes			
13	Von Recklinghausen, 1882	F	55	Jejunum	No	No	No	Died
14	Modrzejewski, 1882	F	27	Clavicular region			No	Died
15	Rose, 1884	M	27	Crural nerve	Yes	No	Paravertebral lymph node	Died
16	Arnozan, 1885	F	31	Right side of neck	Yes	Yes	No	Died
17	Hume, 1886	M	37	Sciatic nerve	Yes		Pleura, lung, liver, humerus	Died
18	Rose, 1886	M	27	Sciatic nerve	Yes	Yes	Lung	Died
19	Pomorski, 1887	M	28	Mediastinum	No		No	Died
20	Heydeweller, 1887	M	45	Popliteal space	Yes	No	No	Died
21	Campana, 1887			Extremity				
22	Westphalen, 1887	F	35	Sciatic nerve	Yes		Lung, pleura	Died
23	Westphalen, 1888	F	45	Fifth cervical nerve	No		No	Died
24	Von Bergmann, 1890	M	54	Axillary and scapular regions	Yes	Yes		
25	Thilow, 1889	M	15	Intercostal nerve?	No		No	Died
26	Thilow, 1889	M	55	Axilla	Yes	Yes		Living
27	Sorger, 1890	M	27	Axilla	Yes			Living
28	Cimmino, 1891	M	42	Sacral region	Yes			?
29	Garre, 1892	F	31	Sciatic nerve	Yes	Yes	Suspicious, no necropsy	Died
30	Arnozan, 1892	F	32	Cervical region				Living
31	Von Gernet, 1892	F	43	Shoulder and region of upper arm	Yes			Living
32	Kohtz, 1893	F	Adult	Wall of duodenum				Necropsy specimen
33	Goldmann, 1893	F	54	Tenth intercostal nerve	Yes, 2	Yes, 2	No	Died
34	Jeanselme and Orrillard, 1894	M	21	Saphenous nerve	Yes			Living
35	Tichoff and Timofeff, 1894	M	42	Popliteal space	Yes, 3	Yes, 2	No	Died
36	Feindel, 1896	M	38	Leg	Yes			Living
37	Finotti, 1896	M	44	Sciatic nerve	Yes	Yes	Yes	Died
38	Seheven, 1896	M	24	Median nerve	Yes, 4	Yes, 3	No	Died
39	Hartmann, 1896	F	48	Crural nerve	Yes			
40	Poncet, 1897	M	50	Thigh	Yes		Yes	Died
41	Habermann, 1898	F	28	Sciatic nerve	Yes			Living
42	Delore and Bonne, 1898	M	34	Radial nerve	Yes, 2	Yes, 2		
43	Girard, 1898	F	50	Thigh	Yes, 3	Yes, 2		Living
44	Girard, 1898	F	40	Hypochondrial region	Yes			Living
45	Vallas, 1899	M	70	Intercostal nerve	Yes, 6	Yes		Living
46	Rolleston, 1899	M	32	Brachial plexus	Yes		No	Died
47	Thomson, 1900	M	28	Median nerve	Yes, 2	Yes, 2	No	Died
48	Adrian, 1901	F	36	Occiput	No		Lung, diaphragm	Died
49	Adrian, 1902	F	56	Duodenum	Yes		No	Died
50	Hulst, 1904	F	19	Cerebellopontine angle			No	Died
51	Hulst, 1904	F	20	Intercostal nerve			No	Died
52	Harbitz, 1909	F	44	Nerve of thigh	Yes, 10	Yes, many		Died
53	Harbitz, 1909	F	22	Sciatic nerve	Yes, many	Yes, many		Died
54	MacKenzie, 1909	M	45	Sciatic nerve	Yes			Living
55	Herrheimer and Roth, 1914	M	38	Nerve of thigh	Yes		Lung	Died

TABLE 1—*Sarcomatous Transformation in Neurofibromatosis—Continued*

No	Author	Sex	Age	Location of Sarcoma	Operation	Local Recurrence	Internal Metastasis	Result
56	Hervheimer and Roth, 1914	M	35	Lumbar plexus			No	Died
57	Wright, 1916	M	Adult	Nerve of thigh				Died
58	Shouldice, 1925	F	41	Stomach	Yes			Living
59	Feriz, 1925	M	64	Thigh	Yes			
60	Hartman, 1927	M	48	Stomach	Yes		Liver, diaphragm	Died
61	Plenge, 1928	M	15	Neck	Yes		Lung	Died
62	Gray, 1929	M	37	Mediastinum			No	Died
63	Gray, 1929	M	25	Sciatic nerve			Lung, pubic bone	Died
64	Potter and McWhorter, 1929	M	22	Occiput	Yes	Yes	Lung, pleura	Died
65	Hosoi, 1930	M	28	Lower cervical and upper mediastinal regions	Yes, 2	No	Suspicious, no necropsy	Died

case illustrates very well the low grade and local nature of the malignant growth, since the patient has been carrying the recurrent growth for the past fifteen years. In Hulst's first case,⁶⁹ there was a bilateral fibrosarcoma of the cerebellopontile angle as well as multiple intracranial neurofibromas. In a case of plexiform neurofibromas of the neck, Plenge⁷⁰ described a spindle cell sarcoma located in the region of the atlas and a mixed cell sarcoma in the region of the submaxillary gland. Does this rarity mean that the presence of a sarcoma has an inhibiting influence on the development of another sarcoma elsewhere in the nervous system? As stated previously, the removal of one sarcomatous growth may be followed by a sarcomatous transformation of another neurofibroma distantly located. Indeed, Cramer⁷¹ has noted in his studies on experimental carcinogenesis that it was rare to find a simultaneous development of malignancy in two or three distant centers of the same area, while it was not uncommon to obtain a successive development in two or even three distant centers after the operative removal of the preexisting malignant tumor. According to his conception of potential malignancy, a large area of cells in a given tissue may be in a condition in which they do not give any manifestation of malignancy either as judged from their histologic appearance or from their biologic behavior, but may, nevertheless, be particularly prone to the development of malignancy when the local inhibitory factors are broken down or shifted. It is interesting to note that Cramer has been able to break or shift these local inhibitory factors by applying a cautery or a caustic pencil to the base of one of the benign growths, which then became malignant in six of the fourteen experiments. Clinically, this

69 Hulst, J. P. L. Beitrag zur Kenntnis der Fibrosarkomatose des Nervensystems, Virchows Arch f path Anat **177** 317, 1904

70 Plenge, K. Ueber eine eigenartige plexiforme Neubildung des Nervensystems in der Gegend des Halses und der Halswirbelsäule, Virchows Arch f path Anat **269** 83, 1928

71 Cramer, W. On Experimental Carcinogenesis. The Local Resistance of the Skin to the Development of Malignancy, Brit J Exper Med **10** 335, 1929

same thing is seen in certain cases when a benign neurofibroma is traumatized by operative procedures

Cases are on record in which operative removal of a painful neurofibromatous nodule may be followed by crops of multiple neurofibromas elsewhere in the body. In spite of repeated operations, no sarcomatous changes occur, as shown by microscopic examination. It is still unaccountable why in some cases a malignant transformation supervenes after a single operation and in other cases even after repeated operations no malignant changes arise. At the age of 36, von Buenger's⁷² patient noticed for the first time a painful tumor the size of a pigeon egg on the right thigh. Operation showed this to be a neurofibroma of the *nevus cutaneus femoris externus*. Gradually, small numbers of painful nodules began to develop along the course of the nerves of the right thigh. A symptomless neurofibroma also developed in the neck, and was removed. At another operation, all the involved nerves in the right thigh were removed in toto. Several months later, similar multiple nodules developed in the other thigh. On removal these were found to be pure neurofibromas. Soon multiple tumors began to appear over the entire body. The patient developed signs of increasing intraspinal pressure and a terminal bronchopneumonia. Necropsy showed that all the spinal nerve roots without exception, the peripheral nerves and the larger part of the sympathetics were involved in the same neurofibromatous process. Microscopically, no malignant changes were found anywhere. This fibromatosis of the sympathetic nerves and ganglions has frequently been observed at necropsy in cases of von Recklinghausen's disease. It has been found that the nature of this enlargement in the sympathetics is precisely similar to that occurring in the cerebrospinal nerves.

From the literature, a total of 65 cases of sarcomatous transformation in von Recklinghausen's disease has been collected. There were 39 male to 24 female patients, or a ratio of 1.6:1. The sex was not stated in 2 cases. As has been pointed out by Alvarez and myself,⁷³ every sex ratio should be corrected by a factor dependent on the sex distribution of the group of men and women studied. Fortunately, Fischer, in 1927, collected 466 cases of von Recklinghausen's disease, of which 299 were men and 167 women, which gives a sex distribution of 1.8:1. Now, since the sex distribution of all cases of von Recklinghausen's disease and of those cases of this disease showing malignant changes is practically the same, it can be statistically stated that sex is of no etiologic importance in cases of sarcomatous transformation. Table 2

⁷² von Buenger, O. Ueber allgemeine multiple Neurofibrome des peripherischen Nervensystems und Sympathicus. *Arch f klin Chir* **55** 558, 1897.

⁷³ Hosoi, K., and Alvarez, W. C. The Influence of Sex on the Incidence of Gastro-Intestinal Disease, *Human Biol* **1** 63, 1930.

shows the age incidence. Seventy-two per cent of the cases occurred in the third, fourth and fifth decades. The youngest was 15 years of age, the oldest 70 years. The age of onset of von Recklinghausen's disease ranged from birth to about 25 years.

In resumé, malignant transformation takes place in about 13 per cent of all cases of von Recklinghausen's disease. When this happens, the tumor grows rapidly and tends to recur locally even after repeated operative measures. Metastasis is usually late and frequently absent, but may rarely occur early. In some cases, the mere extirpation of a malignant tumor or even a benign one appears to stimulate another neurofibroma distantly located to undergo sarcomatous transformation. Prognosis is very poor, the patient succumbing to cachexia and post-operative complications if not to the metastasis.

It is well to bear in mind that not all peripheral multiple tumors in the skin are mesodermal in origin. A few cases have been reported in which multiple ectodermal tumors in the skin closely simulated

TABLE 2—Percentage of Age Distribution in Malignant Transformation

Age periods in years	11-20	21-30	31-40	41-50	51-60	61-70
Percentage	10	21	26	25	15	3

von Recklinghausen's disease. In Anderson and Shennan's case,⁷⁴ the entire face and both shoulders of a 12 weeks old infant were closely studded over with minute growths which proved to be sebaceous cysts. A more striking case is that of Ferreira and Garaude,⁷⁵ who actually counted 276 sebaceous cysts scattered all over the body of a 65 year old man including the head and both extremities. That adenoma sebaceum may occur intermingled with mollusca fibrosa is shown in the case of Anderson⁷⁶ and others. Another type of tumor, neuro-epithelial in origin and hence ectodermal, may produce a more or less striking resemblance to von Recklinghausen's disease. These are the true neuromas of Virchow in contrast to the false neuromas or neurofibromas. In a case of neuroma verum multiplex amyelinicum gangliosum, Knauss⁷⁷ counted more than 60 of these multiple cutaneous nodules, many more were said to be present. Kredel and Beneke¹⁵ counted about 160 of these cutaneous nodules in their case of multiple

74 Anderson, J. S., and Shennan, T. A Neuroblastoma of the Thoracic Cavity, *J. Path. & Bact.* **26** 545, 1923.

75 Ferreira, O., Jr., and Garaude, P. Kystos sebaceous generalizados simulando a doenca de Recklinghausen, *Brasil-med* **2** 343, 1926.

76 Anderson, W. A Case of Adenoma Sebaceum Intermingled with Mollusca Fibrosa, *Brit. J. Dermat.* **7** 316, 1895.

77 Knauss, K. Zur Kenntnis der echten Neurome. Neuroma verum multiplex amyelinicum gangliosum, *Virchows Arch. f. path. Anat.* **153** 29, 1898.

ganglioneuroma of the sympathetics. Among the dermatologists, Levin and Tolmach⁷⁸ and recently Ludy⁷⁹ pointed out that the atypical form of cutaneous neurofibromatosis (those occurring on the extremities and adjacent regions) may be so closely simulated by sarcomas, sarcoids of Boeck-Darier-Roussy, tuberculids and other skin diseases that it is frequently incorrectly diagnosed clinically.

Because of its multiplicity in numbers and its generalized distribution, because of its very frequent association with a multiplicity of congenital abnormalities, and because of its frequent familial character, von Recklinghausen's disease is now generally looked on as a congenital anomaly of the nervous system in a hereditary and dysontogenetic sense. In his review of 466 cases of von Recklinghausen's disease described in the literature, Fischer could find no definite relationship between it and the nevi or pigmented patches. For this reason, the use of the term "incomplete neurofibromatosis" by some dermatologists when only the café au lait spots or melanoderma are present in familial cases is not justified. Levin⁸⁰ and Tucker⁸¹ believed that a definite etiologic relationship existed between endocrine dysfunction and von Recklinghausen's disease. The cases of Kawashima⁸² and of Herxheimer and Roth were associated with a paraganglioma of the suprarenal gland. On the contrary, Schneiderman⁸³ stated that a study of his cases failed to reveal any endocrine dysfunction in the etiology of von Recklinghausen's disease, and that the endocrine glands should not be blamed for the occasional occurrence of tumors in them in association with the neurofibromatosis. At this point, it may be of interest to note that Brickner⁸⁴ described a fibroma molluscum gravidarum in which as many as 40 or 50 sessile and pedunculated fibromas may appear during pregnancy and disappear as rapidly soon after delivery. Lehman⁸⁵ made a plea for a more complete roentgenographic study of

78 Levin, O. L., and Tolmach, J. A. The Atypical Form of Neurofibroma. Its Differential Diagnosis from Other New Growths of the Skin, New York State J. Med. **27** 819, 1927.

79 Ludy, J. B. Cutaneous Neuroma, Arch. Dermat. & Syph. **21** 419 (March) 1930.

80 Levin, O. L. Recklinghausen's Disease. Its Relation to the Endocrine System, Arch. Dermat. & Syph. **4** 303 (Sept.) 1921.

81 Tucker, B. R. Von Recklinghausen's Disease with Special Consideration of the Endocrine Connection, Arch. Neurol. & Psychiat. **11** 308 (March) 1924.

82 Kawashima, K. Ueber einen Fall von multiplen Hautfibromen mit Nebenerengeschwulst, Virchows Arch. f. path. Anat. **203** 66, 1911.

83 Schneiderman, H. Recklinghausen's Disease, Arch. Dermat. & Syph. **12** 483 (Oct.) 1925.

84 Brickner, S. M. Fibroma Molluscum Gravidarum. A New Clinical Entity, Am. J. Obst. **53** 191, 1906.

85 Lehman, E. P. Recklinghausen's Neurofibromatosis and the Skeleton. A Plea for Complete Study of the Disease, Arch. Dermat. & Syph. **14** 178 (Aug.) 1926.

the skeleton in all cases of von Recklinghausen's disease. Are the frequently associated bone changes to be regarded as an integral part of multiple neurofibromatosis, as a consequent event or as additional evidence that some congenital influence is at work? More exact observations must be made before these questions can be definitely answered. In the first case here reported, the many roentgen examinations showed no skeletal defects. Pack⁸⁶ reported a remarkable case of neurofibromatosis of the cranial and deep cervical nerves, presumably unilateral from the symptomatology.

In addition, von Recklinghausen's disease is often associated with one or more other types of tumors. As experience has shown, such multiplicity of tumors connotes an underlying congenital defect. Winestine⁸⁷ pointed out the close relationship that may exist between von Recklinghausen's disease and giant growth and blastomatosis of the intestines. Halbitz reported an unusual case which showed at necropsy a carcinoma of the left ovary with peritoneal and pleural metastases, a large spindle cell sarcoma of the mesentery and molluscum fibrosum. In Takács' patient,⁸⁸ the neurofibromatosis was associated with a large cavernous hemangioma of the right forearm. Girard's third case is unusual in that, following trauma, the skin over a molluscum was transformed into an ulcerating epithelioma. Similar carcinomatous changes over one of the neurofibromas have been described by Schmit⁸⁹ and Chambard.⁹⁰ Patoir and Raviart⁹¹ reported a case of three gliomas of the spinal cord with multiple neurofibromas of the nerve roots. Kaulbach's case⁹² is of much interest in that the multiple neurofibromas of the peripheral nerves were associated with multiple central neurofibromas, multiple gliomatous changes in the spinal cord and a psammoma-sarcoma of the dura mater situated on the rim of the foramen magnum.

86 Pack, G. T. Unilateral Neurofibromatosis of the Cranial and Deep Cervical Nerves. Report of a Case, *Arch Neurol & Psychiat* **21** 919 (April) 1929.

87 Winestine, F. The Relation of von Recklinghausen's Disease (Multiple Neurofibromatosis) to Giant Growth and Blastomatosis, *J. Cancer Research* **8** 409, 1924.

88 Takacs, A. Ueber multiple Neurome, *Virchows Arch f path Anat* **75** 431, 1879.

89 Schmidt, C. Transformation carcinomateuse d'un molluscum, *Franc med* **26** 481, 1879.

90 Chambard, E. Contribution a l'etude de la transformation cancéreuse des néoplasmes bénins de la peau, *Ann de dermat et syph* **4** 61 1883.

91 Patoir, J., and Raviart, G. Gliomes et formation cavitaire de la moelle. Neurofibromes radiculaires. Nevrite des sciatiques. Contribution a l'etude de la lesion dite syringomyelie, *Arch de med exper* **13** 93, 1901.

92 Kaulbach, F. W. J. Ein Fall von multipler Neurofibromatose des peripheren Nervensystems kombiniert mit Fibromen der Nervenwurzeln, Gliomen des Rückenmarks und Sarkomen der Dura mater, *Inaug-Diss., Marburg, 1906*, p. 39.

In a somewhat similar case, recently reported by Penfield and Young,⁹³ the multiple central and peripheral neurofibromas were associated with multiple tumors of the glioma series in the brain and spinal cord and with multiple meningiomas of both the dura and arachnoid. In Orzechowski and Nowicki's case,⁹⁴ in addition to the central and peripheral neurofibromatosis, there were multiple meningiomas of the dura, ependymomas of the spinal cord and medulla and tuberous sclerosis of the cerebral hemispheres. In Funkenstein's case,⁹⁵ a psammoma and an osteopsammoma of the spinal dura were associated with bilateral fibromas of the cerebellopontile angle and multiple neurofibromatosis. Regnier and his associates⁹⁶ believed that they have been unable to find microscopically all "transitions" between the multiple meningiomas and multiple tumors of the acoustic and peripheral nerves observed in their case. In a previous paper,⁹⁷ I found among twenty-two collected cases of multiple intracranial meningiomas, eight cases associated with bilateral fibromas of the acoustic nerve, four of which also showed multiple neurofibromatosis of the cranial and peripheral nerves. At that time, it was stated that the association of meningeal tumors and multiple neurofibromatosis is probably not an *a priori* relationship, but an expression of the predisposition or susceptibility of the person through hereditary and dysontogenetic influences.

SUMMARY

Two cases of von Recklinghausen's disease are here reported in one of which an edematous fibroma of the inferior cervical and upper mediastinal regions became sarcomatous about one year after operative intervention. The microscopic picture indicates that the multiple neurofibromas originated from the perineurium. The literature on the subject of malignant transformation in multiple neurofibromatosis is reviewed.

Drs George E. Beilby and Thomas Ordway permitted me to use the clinical histories of the cases here reported, and Dr William P. Howard allowed me to use the x-ray plates.

93 Penfield, W., and Young, A. W. The Nature of von Recklinghausen's Disease and the Tumors Associated with It, *Arch Neurol & Psychiat* **23** 320 (Feb.) 1930.

94 Orzechowski, K., and Nowicki, W. Zur Pathogenese und pathologischen Anatomie der multiplen Neurofibromatose und der Sclerosis tuberosa (Neurofibromatosis universalis), *Ztschr f d ges Neurol u Psychiat* **11** 236, 1912.

95 Funkenstein, O. Ein Beitrag zur Kenntnis der Tumoren des Kleinhirnbrückenwinkels ("zentrale Neurofibromatose," "Akustikusneurome"), *Mitt a d Grenzgeb Med u Chir* **14** 157, 1905.

96 Regnier, Dechaume, J. Bourrat and Lesbros. Tumeurs meningées et tumeurs des nerfs crâniens. *Ann anat path* **4** 940, 1927.

97 Hosoi, K. Meningiomas. With Special Reference to the Multiple Intracranial Type, *Am J Path* **6** 245 (May) 1930.

CONGENITAL DEFICIENCY OF THE PERICARDIUM

THE FUNCTION OF THE PERICARDIUM ~

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Congenital deficiency of the parietal pericardium is a rare anomaly. Sixty-four cases were collected from the literature by Moore¹ in 1925, and another case was added by Grant² in 1926. The case reported here is the sixty-seventh. Aside from its rarity, this condition possesses a special interest in that these cases throw some light on the function of the pericardium, a subject about which there exists considerable diversity of opinion.

REPORT OF CASE

A colored man, aged 56, was admitted to the Lakeside Hospital on Feb 14, 1929, with the complaint of shortness of breath and swelling of the ankles. Prior to the present illness the patient's general health had been good. There was no history of shortness of breath, precordial pain or edema. The patient always had done heavy manual labor. About one month before his admission to the hospital, shortness of breath had developed. Orthopnea, a productive cough and edema of the ankles developed subsequently. Otherwise the history contained little worthy of note.

The patient was well developed and well nourished. He had serious decompensation. The systolic blood pressure was 260, and the diastolic 140 mm of mercury. Generalized arteriosclerosis was present. The temperature was 37.5 C (99.5 F). The heart was somewhat enlarged, and there was a loud systolic murmur at the apex. The pulse rate was regular, 96 per minute, and after the administration of digitalis it dropped to 60 per minute. Pneumonia developed on the right side, and death occurred twelve days after admission to the hospital.

When the sternum was removed at necropsy, the heart and the left lung lay in a common serous cavity in which there was also about 1,200 cc of clear, light yellow fluid. There was no mediastinal reflection of the parietal pleura on either side of the heart, so that the entire left ventricle was in contact with the left lung. The pericardium was almost completely absent. The ventricles were entirely free from adhesions. A fold of pericardium extended across the base of the heart from the right auricle, to which it was adherent, to the root of the left lung, where it merged with the parietal pleura. This fold was about 4 cm broad and possessed a mesothelial surface adjacent to the heart. It was attached also by a few strands of tissue to the pulmonary artery and to the aorta (fig 1).

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*From the Department of Surgery, the Lakeside Hospital and the Western Reserve University School of Medicine

1 Moore, R L. Congenital Deficiency of the Pericardium, *Arch Surg* **11** 765 (Nov) 1925

2 Grant, R T. Congenital Pericardial Deficiency. An Observation on the Function of the Pericardium, *Heart* **13** 371, 1926

Extending from the hilus of the right lung to the diaphragm was a blind pouch of fibrous tissue having a mesothelial lining and almost completely covering the right auricle. In the illustration this pouch is shown opened, with its wall retracted toward the right lung. It closed off the space between the sternum anteriorly and the vertebrae posteriorly. The right phrenic nerve lay in the base of this pouch on the pulmonary aspect.

Posteriorly, there was a soft collar or pad of areolar tissue and fat extending from the hilus of the left lung across the base of the heart to the lateral aspect of the right auricle to which it was adherent. This structure ended near the junction of the diaphragm and the blind pouch referred to. The superior margin of this collar was adherent to the heart at the atrioventricular junction, and as it curved forward to its attachment to the right auricle it exerted a slight but definite



Fig 1—Anterior view of the heart and lungs. The fold of pericardium extending over the anterior surface of the heart from the right auricle to the root of the left lung is shown cut through and the ends retracted. The blind pouch enclosing the right auricle and venae cavae is incised longitudinally and the fold of pericardium retracted toward the right lung. The right phrenic nerve lies on the pulmonary aspect of this retracted fold.

constricting force just below the tricuspid orifice. The surface of this collar of tissue was smooth and glistening (fig 2).

The surface of the ventricles contained an increased amount of epicardial fat, and over the epicardium at the base there was an increased amount of loose areolar tissue. Toward the apex of the heart the epicardium appeared normal. The heart was free from adhesions, except along the atrioventricular groove posteriorly and the right auricle anteriorly and to the right. The heart was definitely enlarged, the enlargement consisting chiefly in hypertrophy of the left ventricle and slight

dilatation of the right auricle. After being fixed in a diluted solution of formaldehyde U S P (1:10), the heart measured 10.5 cm in its transverse diameter, 14 cm from base to apex and 8.5 cm from its anterior to its posterior surface. It weighed 550 Gm. The thickness of the left ventricular wall varied from 10 to 22 mm and that of the right ventricular wall from 4 to 8 mm. The myocardium grossly showed no abnormality, microscopically there was some hypertrophy of the muscle fibers, some slight patchy fibrosis of the myocardium and some loss of nuclear detail. Then endocardium and the various valve orifices showed no pathologic change.

The aorta and the medium-sized arteries, particularly the renal and the coronary arteries, were definitely sclerotic and showed thickening of the intima in the form

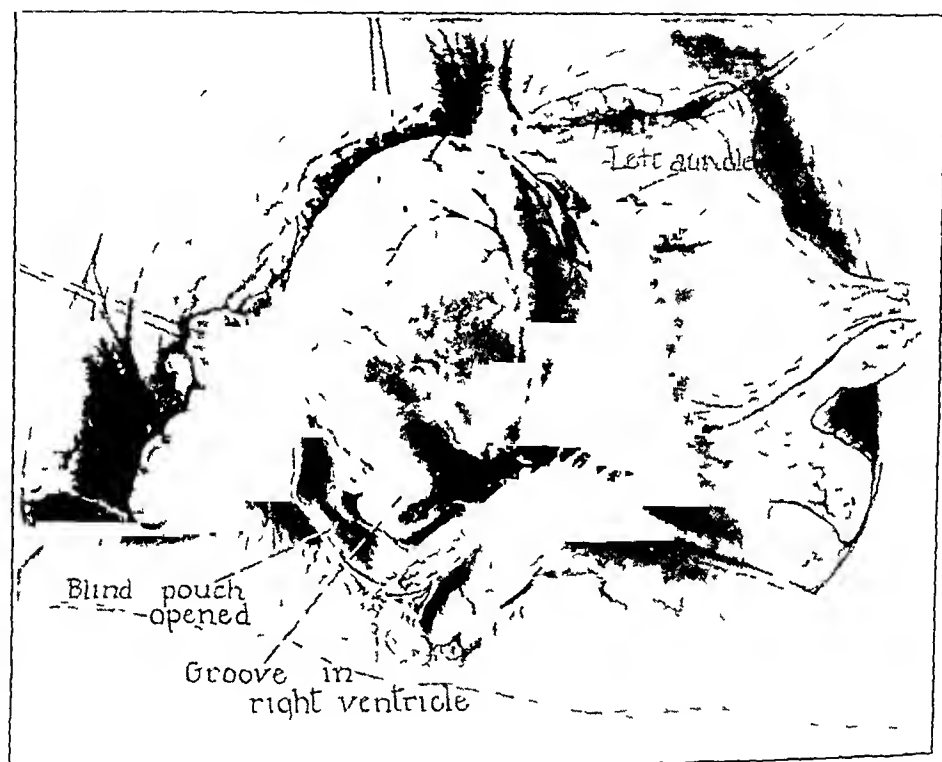


Fig 2—The ventricles are elevated showing the pad of areolar tissue adherent to the atrioventricular junction posteriorly. This pad of tissue extends from the hilus of the left lung to the lateral aspect of the right auricle to which it is adherent. Where it curves forward to its attachment it forms a definite groove in the right ventricle just below the tricuspid orifice.

of elevated pearly gray or yellowish plaques, some of which were calcified. The coronary arteries were widely dilated and showed no evidence of occlusion.

The lung contained a few small areas of consolidation, but in general was air-containing. The right lung was extensively consolidated, and the pleura possessed fibrinous adhesions. The diagnosis of confluent lobular pneumonia was made.

The kidneys together weighed 320 Gm. The capsule was thickened and adherent. The cortex contained a number of stellate scars. Many glomeruli were fibrosed, and the tubules were compressed and atrophic. The vessels were sclerotic. An aberrant renal artery was present on the left side, producing a partial obstruction to the left ureter. The pelvis of this kidney was dilated and contained two calculi.

There was enlargement of the median lobe of the prostate with dilatation and trabeculation of the bladder. The remaining observations were not especially noteworthy.

The case reported was that of an adult who lived fifty-six years and who had done hard manual labor without any cardiac symptoms. Arteriosclerosis and hypertension developed. A pulmonary infection was followed by cardiac decompensation and death. At necropsy the pericardium was absent. There was some enlargement of the heart. Both ventricles were free, but the right auricle was adherent to several rudimentary bands or folds of pericardium. The latter were such that they did not seem to impair the movements of the heart, and its hypertrophy undoubtedly was that associated with hypertension and arteriosclerosis.

THE FUNCTION OF THE PERICARDIUM

Most textbooks of physiology contain little, if anything, concerning the function of the pericardium. Is this fibrous sac, lined with mesothelium and containing a small quantity of fluid essential or even useful for the normal function of the heart? Can it sustain a dilating myocardium or is its presence a potential danger, another of those structures like the tonsils, the appendix or the saphenous veins that well could be omitted from the human anatomy?

In an analysis by Moore¹ of forty-two cases of deficient pericardium, adhesions between the heart and adjacent structures were found in twelve, three of which showed enlargement of the heart. In one of these three cases, reported by Bristowe,³ a valvular defect may have accounted for the hypertrophy. The second case reported by Curling⁴ occurred in a man, aged 46, who previously had been healthy, who died of myelitis and whose heart was found to be rather large and flabby. The third case, reported by Picchi,⁵ was that of a man, aged 60, who died of fibrinous pneumonia, the heart was described as a little larger than normal in volume. Unfortunately, many of the reports of cases of deficiency of the pericardium are incomplete, and an exact analysis of all cases cannot be made. In the case recently reported by Grant² there was a small adhesion between the heart and the lung, but this adhesion apparently had no effect on the heart. Likewise in the present case there were several adhesions to the right auricle and along the atrio-ventricular groove posteriorly, but these adhesions apparently had no effect on the heart. It may be said, therefore, that adhesions between

3 Bristowe. *Malformation of the Pericardium and Left Pleura*. Tr. Path. Soc. London **6** 109, 1854-1855.

4 Curling. T. B. *Case of Congenital Absence of the Pericardium with Observations*. Tr. Med.-Chir. Soc. London **22** 222, 1839.

5 Picchi. *Sperimentale* **61** 375, 1907.

the heart and adjacent structures occur more frequently when the pericardium is defective, but that there was no conclusive evidence in any of the cases that adhesions were the cause of cardiac hypertrophy.

The cases may be analyzed further to determine whether the heart was more prone to undergo either acute dilatation or a slowly developing dilatation when the "sustaining effect" of the pericardium was not present. In an analysis of forty-six cases by Giant,² the size of the heart was not stated in sixteen, ten were in fetuses or children, and of the remaining twenty persons not one died of acute dilatation. Of these twenty cases in adults, the heart was described as normal in ten and as enlarged in ten. Of the ten cases showing enlargement one was associated with syphilis, one with mitral stenosis and one with nephritis, the remaining seven were incompletely reported, so that other possible conditions associated with cardiac enlargement could not be excluded. Among the ten persons with a normal-sized heart, there was no evidence of any cardiac abnormality either in clinical examination or in the history. No case of deficient pericardium was diagnosed clinically, and in no instance was the anomaly of the pericardium regarded as responsible for death or even as having exerted a significant influence.

Experimentally, Barnard⁶ found that the heart without its pericardium ruptured under a pressure of one atmosphere, whereas the pressure required to rupture the heart with the pericardium intact was one and three-fourths atmospheres. From these experiments he concluded that the pericardium was necessary to prevent dilatation of the heart. Kuno,⁷ in experiments with heart-lung preparations, found that the heart without the pericardium could not tolerate a dilating force, and that a slightly increased venous pressure caused hemorrhage in the cardiac muscle. Amerio,⁸ in experiments on rabbits, found that the margin of the pericardium remaining after partial resection in places became adherent to the wall of the chest, but that after total resection of the pericardium no adhesions were found between the heart and the surrounding organs. These procedures, he found, did not affect the life of the animal, and he concluded that in human beings the pericardium, when involved by tumors of the chest wall, could be resected without fear of endangering life. Parlavacchio⁹ performed similar experiments on ten dogs, and noted in each case a pronounced loss of

6 Barnard, H. L. The Functions of the Pericardium, *J. Physiol.* **22** 43, 1898.

7 Kuno, Yas. The Significance of the Pericardium, *J. Physiol.* **50** 1, 1915-1916.

8 Amerio, V. Contributo clinico-sperimentale allo studio delle ferite del pericardio, *Atti d. XI Cong. med. internaz.*, Roma **4** 301, 1894.

9 Parlavacchio. Experimentelle Perikardiektomie und ihre möglichen therapeutischen Anwendungen, *Deutsche Ztschr. f. Chir.* **98** 126, 1909.

weight and observed at necropsy a hypertrophy of the left ventricle. The size of the heart, however, was not observed by roentgen studies. Rehn¹⁰ performed total or partial pericardiectomy on five dogs, and in no case did he observe any effect on the health of the dog. No adhesions were found at necropsy, and no histologic changes were found in the cardiac muscle. Mazzone¹¹ removed the pericardium from seven dogs, and found that the operation had no effect on the animals. Yamada,¹² by making a long incision in the pericardium so as to nullify the effect of the pericardium on the heart, was unable in a series of fourteen dogs to obtain the results of Kuno in heart-lung preparations. During the postoperative period, the dogs were exercised by running. Dilatation of the heart did not occur, and in no case was intramural hemorrhage found. From these experiments, Yamada concluded that the protective influence of the pericardium was not of great significance. In none of the experiments mentioned were the animals subjected to strenuous exercise, and the advisability of studying the capacity of the heart to perform a greatly increased amount of work without its pericardium led Beck and Moore¹³ to carry out additional experiments. Dogs were vigorously exercised, but not visibly exhausted, by swimming in a tank. From these experiments it was concluded that the general health of the dog did not seem to be impaired by pericardiectomy, that the response to exercise did not vary appreciably from the normal, and that dilatation or hypertrophy of the heart did not develop. Following pericardiectomy, it was found that the epicardium usually became covered with a delicate film of areolar tissue which did not seem to impair the function of the heart. Not infrequently a small adhesion extended to the incised margin of the pericardium or to the lung, but such adhesions seemed to be of little significance.

In certain pathologic conditions the pericardium exerts a pronounced effect on the circulation. Experiments by Beck and Holman¹⁴ in which acute plethoria was produced by the intravenous injection of blood and salt solution showed that the pericardium presented a limiting or constricting action to acute dilatation of the heart. In these experiments the pulse pressure doubled and the heart greatly dilated when the peri-

10 Rehn L. Zur experimentellen Pathologie des Herzbeutels, Verhandl. d. deutsch. Gesellsch. f. Chir., 1913, p. 339.

11 Mazzone F. Contributo sperimentale alla pericardiectomia, Centralbl. f. Chir. **39** 1046, 1912.

12 Yamada M. Ueber die Bedeutung des Perikardiums, Mitt. a. d. med. Fakult. d. k. Univ. zu Tokio **16** 527, 1917.

13 Beck C. S., and Moore, R. L. The Significance of the Pericardium in Relation to the Surgery of the Heart, Arch. Surg. **11** 550 (Oct.) 1925.

14 Beck C. S. and Holman, E. The Physiological Response of the Circulatory System to Experimental Alterations. II. The Effect of Variations in Total Blood Volume. J. Exper. Med. **43** 681 (Nov.) 1925.

cardium was opened. Numerous dropped beats and extrasystoles marked the opening of the pericardium and the subsequent dilatation of the cardiac chambers. Whether the pericardium prevents stretching of a diseased muscle fiber to the point at which it no longer can effectively contract is problematic. It is to be noted, however, that in the experiments on acute plethoria the cardiac output greatly increased when the restraining influence of the pericardium was removed. According to the experiments recently reported by Van Liere and Crisler,¹⁵ vagal stimulation resulted in a greater dilatation of the heart after the pericardium had been removed than occurred with the pericardium intact.

In the mechanism of cardiac tamponade the pericardium plays a deleterious rôle on the circulation. Under the influence of a gradually increasing tension the pericardium enlarges to contain either the dilating heart or an increased collection of fluid. As fluid collects in the pericardial cavity the heart decreases in size, the venous pressure rises and the arterial pressure falls. The formation of fluid must take place slowly, so that the pericardium can dilate sufficiently to contain it, otherwise a fatal tamponade results. In no event can the intrapericardial pressure rise above the pressure in the venae cavae.

In adhesive pericarditis the pericardium likewise plays a deleterious rôle. In those cases in which the pericardium is thickened and shrunk, the heart inadequately fills with blood, and its contractility is impaired much as a tight-fitting glove impairs the free movements of the hand. It is in these cases that pericardiectomy gives highly beneficial results.

SUMMARY AND COMMENT

A case of deficiency of the pericardium is described.

An analysis of the cases that have been reported shows that adhesions between the heart and adjacent structures occur more frequently with this anomaly than when the pericardium is present. In no instance was the anomaly of the pericardium regarded as responsible for death or even as having exerted any significant influence on the heart or the circulation. The potential danger of bands of tissue adherent to the heart, however, should not be overlooked.

There is no evidence to indicate that the pericardium exerts a beneficial effect on the acutely dilating heart.

In such pathologic conditions in which a positive intrapericardial pressure occurs or in which cardiopericardial adhesions develop, the presence of the pericardium may constitute a grave danger to the mechanics of the circulation. In the therapy for these conditions surgery has much to offer.

15 Van Liere, E. J., and Crisler, George. The Influence of the Pericardium on Acute Cardiac Dilatation Produced by Vagal Stimulation, read at the meeting of the American Physiological Society, Chicago, March 27, 1930.

THORACOPLASTY AS A METHOD OF TREATMENT IN PULMONARY TUBERCULOSIS

REPORT OF FIFTY-THREE CASES

B N CARTER, M D
CINCINNATI

Surgical collapse of the thoracic wall as a method of treatment for selected cases of pulmonary tuberculosis has come to be regarded as a valuable addition to the usual measures previously employed in combating this disease. During the past five years I have performed fifty-three thoracoplasties. Sufficient time has elapsed in many of these cases to enable one to judge the effectiveness of the operation. In addition, it has been possible to follow all of the cases so closely as to be able to state with accuracy the end-results. Forty-six of these fifty-three cases have been referred to the Surgical Service of the Cincinnati General Hospital by the Hamilton County Tuberculosis Sanitarium.

INDICATIONS FOR OPERATION

The need for close cooperation between the surgeon and internist in dealing with the surgical treatment of patients with tuberculosis is obvious. The end-results of thoracoplasty depend largely on the proper selection of patients, and the surgeon who is so fortunate as to have the advice of a careful and well-trained internist is almost sure to show a high percentage of cures. Thus the figures of the Sauerbruch Clinic¹ show that of thirty-five patients with strong indications and no contraindications, 40 per cent were cured, 51 per cent improved and 6 per cent died, whereas, of forty-three patients with questionable indications and some contraindications, only 14 per cent were cured, 60 per cent improved and 14 per cent died. The commonly accepted indications for thoracoplasty are a chronic fibrous type of tuberculosis with or without a cavity, essentially unilateral in a patient who has shown evidence of good resistance, in whom treatment in a sanitarium has failed to effect a cure and in whom artificial pneumothorax cannot be performed. The inflexible indications to my mind should be (1) evidence of resistance as indicated by fibrous tissue reaction around the lesion with contraction of the wall of the chest and dislocation of viscera (2) the

* Submitted for publication, May 2, 1930.

¹ From the Department of Surgery, University of Cleveland.

¹ Bruner, V., and Baer, G. *Die chirurgische Behandlung der Lungentuberkulose*, Berlin, Julius Springer, 1925.

impossibility of performance of a satisfactory pneumothorax. As a general rule the rapidly progressing caseous types of tuberculosis with little or no formation of fibrous tissue do not seem suitable for operation, although good results have been reported by Hedblom in one such case in which preliminary phrenicotomy was performed, followed by complete thoracoplasty in many stages over a period of seven months. In my series, the average duration of tuberculosis before operation was three years, the shortest time elapsing from recognition of the disease until operation being one year, and the longest ten years.

Claus' epigram, "A good pneumothorax is better than a thoracoplasty, but a good thoracoplasty is better than a poor pneumothorax," about sums up the attitude of most observers at the present time. Certainly, the majority of the members of the medical profession feel that if a satisfactory pneumothorax can be done, a thoracoplasty is not indicated. The reasons for this, briefly, are that pneumothorax is a simple procedure, quickly and easily done, it allows gradual compression of the lung, can be terminated when desired and gives the most complete compression of the lung, in contrast, a thoracoplasty is a major surgical procedure, it gives sudden compression of the lung, it cannot be abolished and does not give the most complete compression. The advantage of thoracoplasty over pneumothorax is that once done, thoracoplasty is permanent, whereas with pneumothorax, it fills with their accompanying dangers and inconveniences have to be carried out over long periods of time. Pneumothorax is associated with certain dangers such as empyema, rupture of the lung, spontaneous pneumothorax on the opposite side and pleural shock, but thoracoplasty also may be complicated by the even graver dangers of shock, infection and aspiration pneumonia. It is not so much a question as to whether or not pneumothorax is preferable to thoracoplasty, for that seems established, but as to when to substitute thoracoplasty for pneumothorax. In this connection, the results of Matson² and his co-workers are of interest. In a series of 492 cases in which pneumothorax was attempted the following results were obtained: (1) complete collapse in 43 per cent, or 211 cases, with clinical recovery in 48 per cent, the condition arrested in 20 per cent and death in 21 per cent, (2) partial collapse in 37 per cent, or 183 cases with clinical recovery in 13 per cent, the condition arrested in 13 per cent and death in 50 per cent, (3) no collapse obtainable in 20 per cent, or 98 cases with recovery in 7 per cent, the condition arrested in 23 per cent and death in 55 per cent. Swezey and Schonbar,³ in reporting on 207 cases (205 of tuberculosis) in which pneumothorax was done over a period of ten years, found that successful collapse could

2 Matson, R. C., Matson, R. W., and Bisillon, M. *Tubercle* 7 12, 1925

3 Swezey, S., and Schonbar, Alexander. *Am. Rev. Tuberc.* 13 156, 1926

be obtained in 38 per cent, partial collapse in 36 per cent, and that in 26 per cent collapse could not be obtained, their mortality figures are much like those of Matson and his co-workers. Mattill and Wall⁴ stated that of 150 patients on whom pneumothorax was attempted, no free pleural space was found in 37, of these, 19 were subjected to thoracoplasty, with the result that 4 died, 4 are working and 11 are under treatment, of the 18 who were not operated on, 7 died 1 is working and 10 are under treatment. Judging from these reports which are probably representative of the usual experience, pneumothorax can be effectively employed in only about 40 per cent of the cases, and whereas the percentage of deaths is approximately 20, if pneumothorax is complete, it is about 50 when pneumothorax is partial or impossible. It would seem, therefore, that in a case suitable for collapse therapy, but in which this may not be thoroughly accomplished by pneumothorax, it is far safer to do a thoracoplasty, and this should be done early, and not as a last resort. The instances in which thoracoplasty is preferable to pneumothorax have been well stated by Davies⁵ as follows:

(1) In the long standing chronic cirrhotic type of pulmonary tuberculosis which is associated with great shrinkage of the lung and consequently displacement of the mediastinum and with considerable and generalized dilatation of the bronchial tree. (2) In cases with large thin walled or very thick walled cavities. In the former the danger of rupture in the pneumothorax is great. In the latter it is very improbable that the pneumothorax can produce an efficient collapse.

The same author stated that thoracoplasty should replace pneumothorax:

(1) When adhesions are present which are interfering with the efficient collapse of the lung. The exception to this is when the adhesions are basal only. (2) Where there is a thin walled cavity held open by an adhesion or adhesions too broad for division by cauterization with safety. (3) When there is a thick walled cavity which cannot be collapsed by reason of the rigidity of its walls. (4) When there is an effusion which is persistent and is responsible for, part at any rate, of the febrile condition. (5) When there is a bronchial fistula. (6) When the lung is creeping out or has crept out and the symptoms are recurring, and the reexpansion is too great to be dealt with by phrenic evulsion only.

Six of my patients had had a pneumothorax (artificially induced) which was not satisfactory owing to the accumulation of thick tuberculous pus in two cases, to an uncollapsed cavity in two, and to a combination of each of these in two. They have all done unusually well and are now classed as apparently well. They stood operation better than the usual patient. The degree of collapse of the thoracic wall was excellent and the pleural cavity has been well obliterated in all.

⁴ Mattill, P. W. and Wall, M. H. *Am. Rev. Tuberc.* **13** 537, 1926.

⁵ Davies, H. M. *Tubercle* **7** 437, 1925.

The indications for thoracoplasty admitting of variations are the condition of the opposite lung and the general condition of the patient. In the all important question of the good lung, the internist who has been familiar with its appearance in the roentgenogram and the physical signs over a period of months, can and should bear the burden of the decision. There are very few cases of absolutely unilateral pulmonary tuberculosis, and nearly all cases coming to operation show some degree of involvement on the opposite side. Lesions on the good side which seem of serious nature to the surgeon seeing the patient for the first time, in the light of the internist's knowledge, may not be contraindications to operation. The latter may know that such lesions have been stationary for weeks or months, or that they are becoming more fibrous or that they may be due to circulatory changes. Active caseous lesions on the good side are definite contraindications to operation. Inactive, fibrotic lesions or less fibrotic ones that have been stationary are not contraindications. Other things being equal, lesions situated in the apex of the good lung are less serious contraindications than similar sized ones in the base or hilus. The explanation usually given for this is that the excursions of the lung are greater at the base than at the apex, and that the hilus, being in proximity to the heart, is kept in almost constant motion, consequently, lesions in these locations are more apt to be activated when increased work devolves on the good side, following collapse of the bad.

Changes occur so quickly in the more affected side, that no patient should be operated on unless careful physical and roentgen examinations are done just before the operation. In one of my cases, in which this was neglected, I have reason to believe that changes contraindicating operation had occurred within ten days following the last roentgen examination and were unrecognized, with disastrous results. In another, a roentgenogram made two weeks before the proposed operation showed the good side clear, but one made the day before that set for operation, showed contraindicating changes. The operation was deferred for six months, the lesions receded or became fibrosed and operation was successfully done.

The desire to extend the indications for operation is unusually strong in the case of these patients whose only hope lies in surgical collapse of the lung, and physicians are tempted to take desperate chances. In doing so, I feel that it simply makes the patient's end more painful and tends to discredit the operation. By means of operations divided into more than the usual two stages and preceded by phrenicotomy good results may be obtained in cases that would otherwise be fatal. I feel that one of my patients who died could have been saved, had she had a phrenicotomy first, and then a several stage operation rather than the

accustomed two stages. By closest attention to detail before operation, patients who at first glance seem unable to stand the ordeal, may be gotten into satisfactory condition for it. The greatest aid here is the use of transfusion. This has been emphasized by Yates⁶ and we heartily agree with him as to its use both preoperatively and postoperatively. I have used it in nine cases in this series, three transfusions were given in two of these one before each stage of the operation. In every case but one the results of transfusion were remarkable.

Attention to several details in the preoperative treatment will be followed by greater ease of operation, fewer complications and better results. It is advisable to have the patients under observation for several days in the hospital where the operation is to be performed. The excitement of being transported to a new hospital, the fatigue or exposure on the journey may cause a flare-up of temperature and pulse, in the presence of which the added strain of operation might be dangerous. Practically always, these patients, ill and toxic for a long time, have a myocarditis and a treatment with digitalis should be given before operation. This precaution was disregarded in some of my first cases and the contrast in their cardiac reaction was striking in comparison to the later ones in which digitalis was used. Patients with appreciable amounts of sputum should be made to empty their cavities by postural drainage just before operation, to guard against aspiration during or immediately after the collapse of the thoracic wall. It is imperative that the skin be free of abrasions, acne, etc., before operation is attempted. Probably the most important precaution preoperatively is to match the patient's blood for transfusion. So frequently, the long illness has depleted the patient's reserve and has brought about such an anemia, that they are especially poor risks. It is remarkable what a difference one or two transfusions will make in the patient's condition, and I am sure that by using them freely, certain patients who would otherwise succumb can be gotten safely through the operation.

ANESTHESIA

The tendency at present is toward general anesthesia for cases of thoracoplasty, but nevertheless, we favor and use local anesthesia. Archibald⁷ has given up the use of local anesthesia for a combination of gas and oxygen and local anesthesia. Sauerbruch⁸ uses ether in patients whose expectoration of sputum in twenty-four hours is less

6 Yates J. L. Rationale of Operations Helpful in Promoting Recoveries from Pulmonary Tuberculosis. *Arch. Surg.* **14** 369 (Jan.) 1927.

7 Archibald, E. *Am. J. Surg.* **10** 328, 1925.

8 Sauerbruch, F. *Die Chirurgie der Brustorgane*, ed 2, Berlin, 1920, vol. 1.

than 30 cc Chaher⁹ stated that he used rectal anesthesia Meyer¹⁰ seems to feel that local anesthesia is safest General anesthesia is certainly open to the serious objection of aspiration of the contents of cavities, so frequently present, into other portions of the same or opposite lung This constitutes the greatest danger during the operation, and we feel that any procedure that will tend to decrease its incidence is well worth while One of my patients died of pneumonia in the good lung, which I felt was the result of a light gas and oxygen anesthesia The objections usually made to the local anesthesia are that it is frequently unsatisfactory, it is time-consuming, and poisoning from procaine hydrochloride with death may result, and that it is too great a mental strain on the patient and surgeon I have used local anesthesia in fifty of the fifty-three cases, and still feel it is the method of choice A combination of light nitrous oxide gas and local anesthesia was used in three cases The method used has been direct infiltration of the skin and muscles and injection of the intercostal spaces close to the spine under direct vision The intercostal nerves are injected as soon as the spaces are exposed and by the time a few vessels have been tied off and the soft tissues reflected laterally, the anesthesia is complete I have had one case in which local anesthesia was unsatisfactory and had to be abandoned in favor of light gas and oxygen The infiltration can be done rapidly, the usual time required in my cases in which the anesthesia is used, is about fifteen minutes There have been no cases of serious poisoning with procaine hydrochloride, although in one instance it was felt wise to terminate the operation after resecting three ribs owing to a reaction attributed to the procaine hydrochloride One per cent procaine hydrochloride is used for the skin, 0.5 per cent for the soft tissues and 1 per cent for the intercostal nerves Matson¹¹ has shown that in injecting solutions into the intercostal spaces close to the spine, not infrequently some of the solution is found inside the dura He expressed the belief that this may be the cause for some of the deaths and reactions attributed to procaine hydrochloride It is quite true that local anesthesia imposes a more severe mental strain on the patient, and this is its worst feature However, by preliminary administrations of morphine and by encouragement from a cheerful and tactful nurse during operation, a good deal may be done to lessen it Although it is more trouble and is harder on the operator, the fact that it is safer should overbalance these more or less minor objections to its use

9 Bonniot *Presse med* **32** 1012 (Dec 17) 1924

10 Meyer, Willy Anesthesia in Extrapleural Thoracoplasty for Pulmonary Tuberculosis *Arch Surg* **14** 432 (Jan) 1927

11 Matson, R C, Bisullon, M, and Matson, R W *Tubercle* **7** 65, 1925

OPERATION

The standard Wilms-Sauerbruch thoracoplasty is so well known at present that it is not necessary to go into its details. This is the procedure used by the majority of surgeons today who are operating on patients with pulmonary tuberculosis. Although there are many modifications, they are for the most part minor departures from the standard operation such as variation in the length of the rib resected, which rib is divided first and whether the lower or upper half of the chest is attacked first. Thus Brauer¹² resects greater lengths of rib beneath the scapula than other operators. Bull¹³ does an apicectomy beneath the three upper ribs before dividing them. John Alexander¹⁴ recommends phrenicotomy followed by resection of only the upper seven ribs etc. There seems to be a unanimity of opinion on the following points: (1) the division of the ribs close to their articulation with the spine, (2) resection of a portion of the first rib, (3) resection of longer portions of the ribs than Wilms advocated. Archibald's¹⁵ method of fitting the amount of rib resected to the condition in the individual case has seemed most logical to me and that has been the method used in this series. In general however I resect 10 cm. of the eleventh rib, from 12 to 15 cm. of the tenth to the fourth ribs inclusive, 10 cm. of the third rib, 8 cm. of the second rib and from 3 to 5 cm. of the first rib. Of the 53 patients in this series 26 had segments of the first to the tenth ribs inclusive resected, 19 had portions of the first to the eleventh ribs inclusive, 2 had the first to the twelfth ribs inclusive and 3 had the first to the ninth ribs inclusive. In the first few cases I made a curved incision out under the scapula for the second stage, but have abandoned it and now prolong the lower end of the second incision into the upper end of the first. My average for the total length of rib resected has been 115 cm. for 11 ribs and 125 cm. for 11 ribs. I always resect the first rib and usually the eleventh, though if the diaphragm is high, if a preliminary phrenicotomy has been done or the lower lobes are relatively free from disease, I leave the eleventh rib intact. Owing to the fact that the contraction of the fibrous tissue in the lung on the side on which the operation has been performed is the most potent factor in producing the collapse, following resection of the ribs, greater lengths of rib should be resected in cases in which there is relatively much scar tissue in the diseased lung. It is interesting to note the varying amount of collapse in the different portions of the same lung, the collapse being more marked over the portions containing the greatest amount of fibrous tissue. Where there is little fibrous tissue in the lung and pleura and

12 Brauer, L. Beitr. z. Klin. d. Tuberk. **51** 319, 1922

13 Bull, P. Proc. Roy. Soc. Med. **17** 1, 1924

14 Alexander, John. Ann. Surg. **81** 748, 1925

consequently, greater mobility of the mediastinum, the danger of flapping mediastinum with its resulting circulatory and respiratory embarrassment should be guarded against by resecting shorter segments of ribs, and by dividing the operation into more than the accustomed two stages. I have advocated removal of portions of the first to the tenth ribs or the first to the eleventh ribs whenever a thoracoplasty has been advised and partial thoracoplasties have not been done. Though I have not had experience with the latter, I have felt that the amount of lung conserved by it is not comparable with the greater degree of collapse obtained by the resection of portions of all the ribs. All of my patients have had the portions of the lower ribs resected first, followed in about two weeks by resection of portions of the upper ones. Except for six cases, preliminary phrenicotomy has not been done. However, now I believe it advisable in nearly all cases, and especially those in which (1) it is uncertain whether the good lung will stand the added strain thrown on it by thoracoplasty, (2) the patient's general condition is such that it is questionable whether he can stand thoracoplasty in his present state, phrenicotomy being done to lessen fever, improve the general condition, and (3) in which it is possible that phrenicotomy alone may effect a cure.

The operative procedure used in this series of cases varies in several respects from those reported from other clinics. One gets the impression from the literature that the operations must be done with extreme rapidity, as though the time element was a great factor in their success. It has been my opinion that an operation done only as rapidly as is compatible with gentle handling of tissues, with accurate hemostasis and absence of tearing and tugging, is far safer, is attended with less shock, and more quickly recovered from, than one done under conditions where much has to be sacrificed to the demands of speed. The average time in my cases is about an hour. The patients are placed in a supine position on the operating table, with the arm on the affected side hanging over the edge so it can be moved to throw the scapula out from the thorax. As soon as the skin is incised, towels are fastened to the edges of the wound with small metal skin clips. This can be done rapidly and prevents slipping better than any method we have tried. Gentleness in handling tissues and accurate hemostasis are insisted on. Fine silk has been used for ligatures and suture in all but one case and that wound became infected. No case has been drained and only three have filled with blood or serum to a degree necessitating aspiration. All the operations have been done in two stages, from below up, save five, which were done in three stages. Two of these were in emaciated patients who expectorated from 4 to 6 ounces of sputum a day, had tuberculous laryngitis and were in poor general condition. One other was in an

emaciated woman, aged 42, whose condition became alarming after three ribs had been resected, so that the operation was terminated and two later stages done. In the other instances, the presence of dangerous lesions on the good side made a three-stage resection preferable so as to more gradually throw added strain on the good lung. Preliminary phrenicotomy has been used only six times although I now believe it should have been done in many of the other cases. The usual interval between operations has been two weeks, in some cases, for various reasons, the operation has been done with intervals of 10 days and in others intervals of over two weeks. If there is any doubt as to the patient's ability to stand the second operation it is wiser to wait longer than to regret a too hasty second stage.

No serious accidents have been met with during operation. The pleura was torn in two cases but was immediately sutured and reinforced with intercostal muscle. No ill effects resulted and the wounds healed without complications. One patient had a severe reaction, which I thought due to procaine hydrochloride as mentioned before. The first rib was very difficult to expose in several cases. I have not been troubled with alarming degrees of shock either during or after operation in any case, although several patients have exhibited mild degrees as evidenced by pallor, slight sweating and rapid pulse. It is remarkable how well the patients stand this major procedure if properly prepared and if the operation is done without loss of blood and without undue traumatism to tissues.

POSTOPERATIVE CARE

The postoperative management resolves itself largely into preventing aspiration pneumonia and into maintaining the resistance of the patient. The first forty-eight hours are the most trying and dangerous, for it is then that aspiration is most apt to occur owing to the difficult and painful attempts at coughing. The frequency of the cough should be controlled by morphine which also relieves the pain to such degree that when coughing takes place it can be effective. Every effort is made to have the patient expectorate the secretions when he begins to cough. Firm pressure on the operated side during coughing spells and a very snug dressing help greatly to accomplish this.

The general resistance is maintained by forcing fluids, by partaking of nourishing food, by rest (sedatives) and by transfusion, if other methods fail. I believe that many lives will be saved by transfusions made before and after the operation. Mediastinal flutter and paradoxical respiration are the most serious sequelae of the operation. They are apt to occur in patients with a thin pleura. Consequently, in this type of case where, as aforementioned, shorter portions of ribs should be resected, it is safer to do the operation in three stages. In this series

one patient died from these causes on the second day after the operation. She was extremely well nourished, in good general condition and had a small cavity at one apex with the rest of the lung relatively clear. It was decided to resect the upper eight ribs at one operation. The pleura was so thin that the lung could be seen moving beneath. The patient stood the operative procedure well but in a few hours developed a rapid pulse, cyanosis, pallor and dyspnea. In spite of all that could be done, she died in thirty-six hours.

The temperature of patients who do well is usually elevated from one to three degrees for the first two days, then falls steadily, reaching the preoperative level in about one week. This is thought to be due to a flooding of the body with toxins from the collapsed lung, it may be likened to a large injection of tuberculin. Bull¹³ and Graf¹⁵ have found that blood taken from patients in the febrile stage after thoracoplasty is much more toxic to tuberculous guinea-pigs than that of the same patient when taken before operation. When the temperature remains high, or becomes more elevated, the explanation usually lies in infection of the wound or extension of the disease to other portions of the lung on the same side, or to the opposite side by aspiration, this was true in both of our cases in which aspiration pneumonia developed on the opposite side. There is much less reaction following the stage in which the upper ribs are resected. If the patient has stood the resection of the lower ribs, I feel no alarm as to his ability to go through the second stage. It is largely for this reason that we resect the lower ribs first, for as it is the greater strain of the two, the patient has a better chance of standing it when his resistance is at its highest, i. e., before there has been any operative procedure. The pulse in general follows the temperature. Where digitalis has been used before and after operation I have found much less cardiac reaction. Nearly every case shows slight dyspnea or cyanosis for a few days after operation. Marked cyanosis and dyspnea mean usually a flapping mediastinum but may result from aspiration pneumonia in the good lung. I have seen it three times in my cases. In two instances there was tuberculous pneumonia in the good lung and in the other there was mediastinal flutter. The dressings are undisturbed for five days, at which time the sutures are removed and a tight dressing applied for another week.

RESULTS

Fifty-three patients have been operated on in the past six years a total of 108 operations (45 cases in two stages, 5 cases in three stages and 3 cases with only one stage completed). Forty-four patients

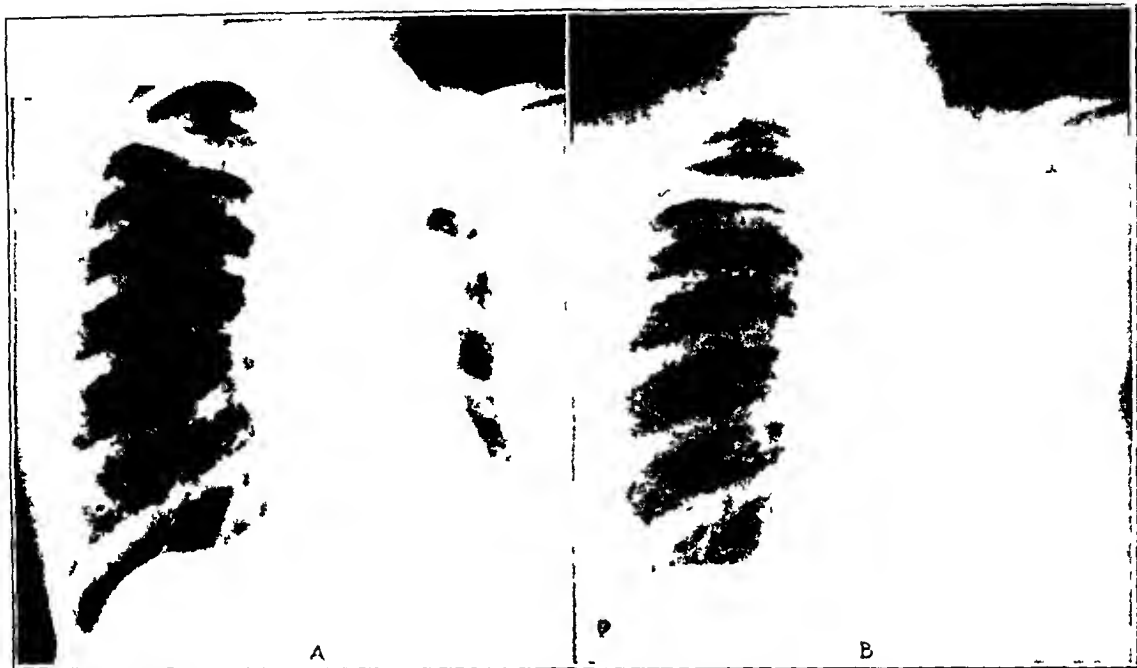


Fig 1—H H Roentgenograms showing (A) large cavity at the apex of the left lung, (B) result one year after thoracoplasty

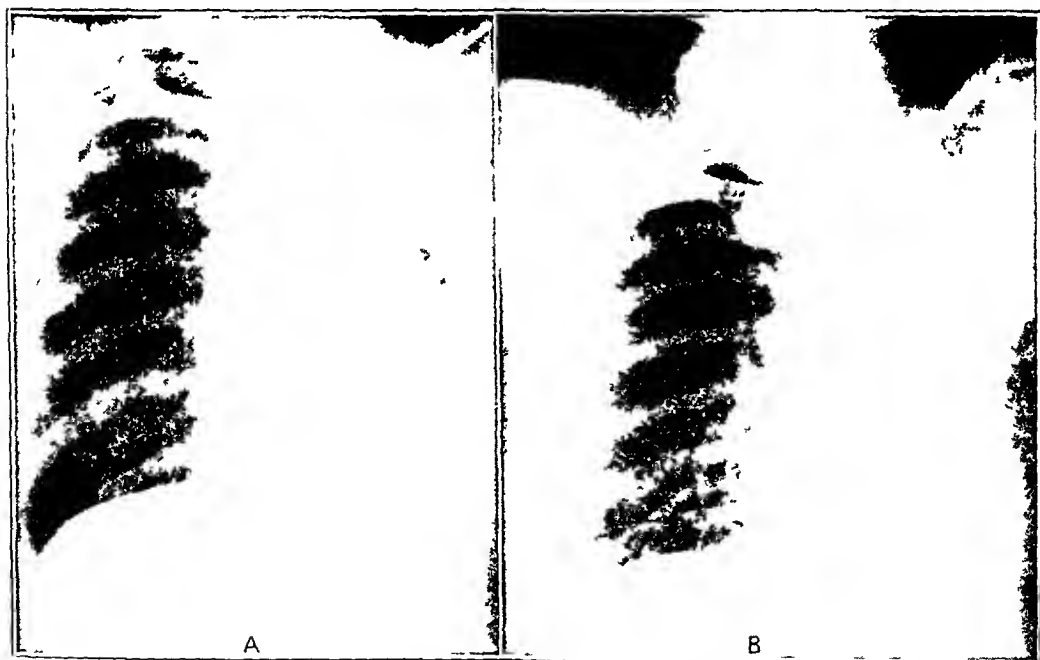


Fig 2—M J Roentgenograms showing (A) multiple cavities and considerable fibrosis on the left, (B) results two years after operation

(83.01 per cent) are alive today, 9 (16.99 per cent) have died. Table 1 gives the results to date in the 53 cases. In this table "apparently well" indicates that the patient has a sputum that is negative for tuberculosis.

TABLE 1—Results in Fifty-Three Cases

Year in Which Operation Was Performed	Number of Cases Done	Apparently Well	Condition of Patient at Present			
			Improved	Unimproved	Too Early to Classify	Dead
1924	1					1
1925	5	3				2
1926	13	9	1*	1		2
1927	11	9				2
1928	9	6	3†			0
1929	14	8	1‡		3§	2
Total	53	35	5	1	3	9

* This patient, a girl, was 16 years of age when she was operated on four years ago. She is sk. thin and anemic with a huge cavity occupying nearly the whole upper lobe. She has been obliterated, the sputum was negative for tuberculosis bacilli on three occasions. The patient was apparently well for two years, but has recently been feeling tired, has been coughing more and was put to bed two months ago. I believe she will recover, and if she is careful, live comfortably for years.

† One of these three patients had a huge cavity in one apex which, according to a roentgenogram, has disappeared, though actually I believe it is present, but small. The patient looks healthy, feels well and feels that he is cured. Except for an occasional positive sign of tuberculosis bacilli in the sputum, he could be classed as "apparently cured." Another is a woman, aged 40, with a very thick walled cavity which has not been entirely collapsed. She looks and feels well but still has a few tuberculosis bacilli in her sputum. The last patient of the three is a boy who was 18 when the operation was done. He was a poor risk and had his operation in three stages, with several transfusions between. His lung showed several cavities in upper and middle lobes. He looks and feels much better, has a moderate cough, but his sputum shows a few bacilli.

‡ This patient is a man, aged 38, who has been sick for six years. The whole upper lobe on the left was a huge cavity. The cavity has been decreased to about one tenth its previous size but is still present. The patient shows positive signs of tuberculosis bacilli in the sputum. Further operative procedure is to be done in an effort to collapse the cavity completely.

§ These three patients all have sputum that is negative for tuberculosis bacilli and seem on their way to recovery, but it is too early to say what their end result will be, as they have been operated on only three months ago.

TABLE 2—Summary of Ages, General Condition and Sex of Patients and Side of Operation

Recovered									
Age						General Condition			
15 to 20	21 to 25	26 to 30	31 to 35	36 to 40	41 to 50	Good Risk	Moderate Risk	Poor Risk	
4	15	6	9	5	5	30	9	5	Male 15 Female 29 Right 19 Left 25
Died									
Age						General Condition			
21 to 25	26 to 30	31 to 35	36 to 40	41 to 50	51 to 60	Good Risk	Moderate Risk	Poor Risk	
5	1	2	1	1		3	2	4	Male 4 Female 5 Right 4 Left 5

bacilli is free from cough, and is leading a normal life, "improved" means that the patient has sputum that is occasionally positive for tuberculosis bacilli, has gained in weight and strength and is able to be up and about but has to take unusually good care of himself.

In table 2 is found a summary of the ages of the patients operated on, their general condition, sex and side of operation.



Fig 3—H L Roentgenograms showing (A) huge cavity at the apex of the left lung (B) result eighteen months after thoracoplasty

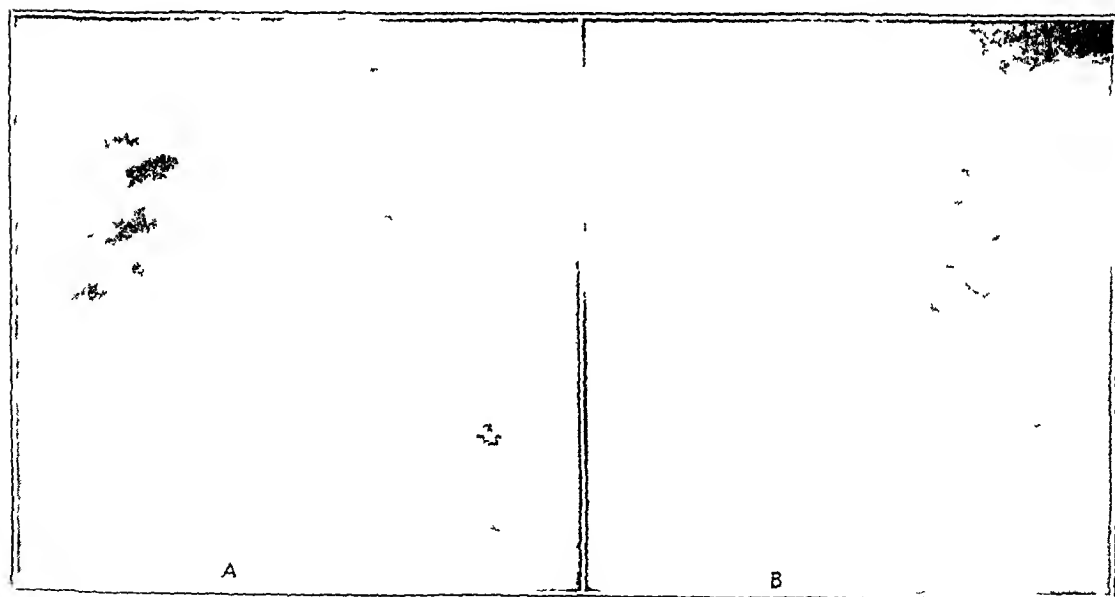


Fig 4—W L Roentgenograms showing (A) artificial pneumothorax with repeated accumulation of thick fluid showing many tubercle bacilli, (B) result one year after thoracoplasty

It is our plan to deal with the pathologic condition of the "good" and the "affected" lungs in a separate communication which will be published shortly. Table 3 gives a very crude idea of the condition of the affected lung in this series.

There was evidence of extrapulmonary tuberculosis before operation in seven of the fifty-three patients. Three of these patients have died. Their lesions consisted of laryngitis, cervical adenitis and gastro-intestinal and laryngeal tuberculosis in the last. In the four patients who are classed as "apparently well," the extrapulmonary lesions were rectal fistula in two cases, and epididymitis in two.

Nine deaths have occurred in this series, an analysis of each death follows.

CASE 1—S. M., a woman, aged 24, ill for one year with tuberculosis was moderately well nourished. She became slightly cyanotic on little exertion. She had a history of digestive upsets, vomiting and alternating attacks of diarrhea.

TABLE 3—*Condition of Affected Lung*

	Living	Died
Cavity	7	
Cavity and caseous bronchopneumonia	15	5
Cavity and marked fibrosis throughout the lung	10	4
Cavity, fibrosis and fluid	4	
Fibrosis	1	
Fibrosis, fluid and caseous bronchopneumonia	1	
Artificial pneumothorax unsatisfactory		
(a) Cavity uncollapsed	2	
(b) Fluid thick, purulent with many tuberculosis bacilli	2	
(c) Combination of a and b	2	

and constipation with slight hoarseness at times. Roentgenograms showed a huge cavity at the apex of the left lung with much caseous bronchopneumonia below it. The right lung showed "fans" resembling caseous bronchopneumonia in the first and second interspaces trunks. There was very little fibrosis on either side. Six ounces of sputum were expectorated in twenty-four hours. This was the first case of the series. Thoracoplasty in two stages was done in August, 1924, the huge cavity was not entirely obliterated by operation. The patient improved for two months, then showed increasing gastro-intestinal involvement, and died five months later with evidences of tuberculous involvement of meninges, kidneys and intestines. In the light of our present knowledge, she was a poor subject for the operation owing to her lack of resistance as evidenced by little fibrosis and the rapidity of the progress of the disease, exudative lesions in the good lung and the extrapulmonary involvement.

CASE 2—M. G., a woman, aged 40, had been ill for five years with tuberculosis. She was thin and weak, and became slightly cyanotic and dyspneic on exertion. There was no history suggestive of extrapulmonary tuberculosis. Roentgenograms made three weeks before operation showed a large cavity at the apex of the left lung with considerable fibrosis and dislocation of viscera, the right lung was essentially clear. She expectorated 4 ounces of sputum in twenty-four hours. The temperature was 102° F. daily. Thoracoplasty was done in two stages in November, 1925. A good collapse ensued. Roentgenograms made ten days after



Fig 5—Photograph showing the two separate incisions for the two stages of thoracoplasty. This has been discarded for the incision shown in figure 6.

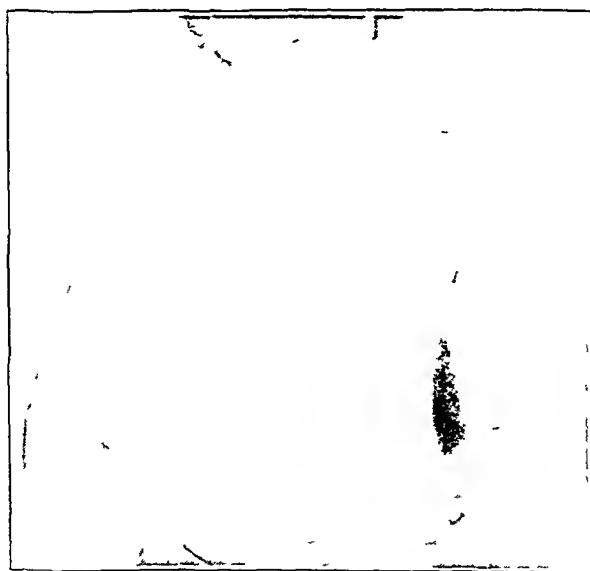


Fig 6—Photograph showing the type of incision now used.

the first operation showed tuberculous caseous pneumonia in the lower lobe of the good lung. The patient died three months after operation from extensive involvement of the good lung. I feel that we should have had a roentgenogram immediately before the operation, and not have relied on the one done three weeks before. Had we done so, I think we would have found enough tuberculous involvement of the good lung to have contraindicated operation. Provided there was no involvement of the good lung before operation the case would have been much better handled had we done a preliminary phrenicotomy and a three-stage thoracoplasty with a transfusion between each stage.

CASE 3—G P, a woman, aged 39, had been ill for one year with tuberculosis. She was thin, but a moderately good risk. She had temperature of 102 F each afternoon, and a pulse rate of 120. Roentgenograms showed cavities in upper part of the left lung, fibrosis with retraction of ribs and dislocation of the viscera. The good lung showed fibrosing lesions in the second interspace trunk, 3 ounces of sputum was expectorated in twenty-four hours. A preliminary phrenicotomy was done in December, 1925, and one week later the temperature had fallen from 102 to 100 F each afternoon. A partial thoracoplasty (tenth to sixth ribs, inclusive) was then done under local and gas anesthesia. The patient was so apprehensive that gas had to be used. Following operation, the temperature rose to 103 F and remained up each day. A roentgenogram showed extensive tuberculous pneumonia on the good side, and the patient became progressively worse, dying in May, 1926, six months after operation. Autopsy showed ulceration in the cecum and ileum and extensive cavitation and caseous bronchopneumonia throughout both lungs. This patient died from involvement of the good lung following operation possibly due to aspiration during the operation while under gas anesthesia.

CASE 4—W W, a man, aged 53, had been ill with tuberculosis for one year. He was moderately well nourished, had a normal temperature, and tuberculous laryngitis which was healing. Roentgenograms showed a cavity at the upper part of the right lung, with considerable fibrosis and dislocation of viscera. The good lung showed a large area of fibrosis, the site of an old cavity which appeared healed. The patient was operated on in three stages under local anesthesia, and a good collapse of the lung followed. He did well for six months, but died ten months after operation from an extension of the disease to, or a lighting up of the old process, in the good lung.

CASE 5—C C, a man, aged 23, had been ill for two and one-half years with tuberculosis. Phrenicotomy was done in October, 1925. Improvement followed until July, 1926, when cavitation began to appear in the affected lung and the good lung showed several small areas of caseous bronchopneumonia in the apex. By November, 1926, these lesions in the good lung had become fibrosed. Thoracoplasty in two stages was done in November, 1926, and the patient had an uneventful recovery. Six months after operation tuberculosis of the spine and kidneys developed, and he died of generalized tuberculosis twelve months after operation.

CASE 6—G P, a man, aged 49, had been ill for nine years, he was emaciated, weak with frequent cough and expectoration of several ounces of sputum a day. He had an active tuberculous laryngitis and a few enlarged cervical glands. Roentgenograms showed marked fibrosis in the right lung with much contraction and a large cavity at the apex. The good lung showed marked fibrosis and calcification, there was no activity. Owing to the marked emaciation and weakness, a three-stage thoracoplasty was done in August, 1927, with a transfusion between each stage. The patient stood the operative procedure well. The laryn-

gitis improved for several months then flared up, and the patient succumbed nine months after operation with evidences of a generalized tuberculosis

CASE 7—M P, a woman, aged 21, was very well nourished and in excellent condition. She had been ill with tuberculosis for two years, and under sanitarium regimen had improved remarkably. All that remained of an extensive tuberculosis was a small thick-walled cavity at the apex of the right lung. The remainder of the lung fields had cleared up entirely. A thoracoplasty involving the first to the seventh ribs was done under local and gas anesthesia in one stage. The pleura was very thin, and the lung could be seen moving to and fro beneath it. The patient's color was bad at the close of the operation, but the pulse was good for twenty-four hours. Typical paradoxical respiration and mediastinal flutter developed, and she died forty-eight hours after operation. I feel now that when it was seen how thin the pleura was, shorter segments of rib should have been removed and only three or four ribs done instead of seven.

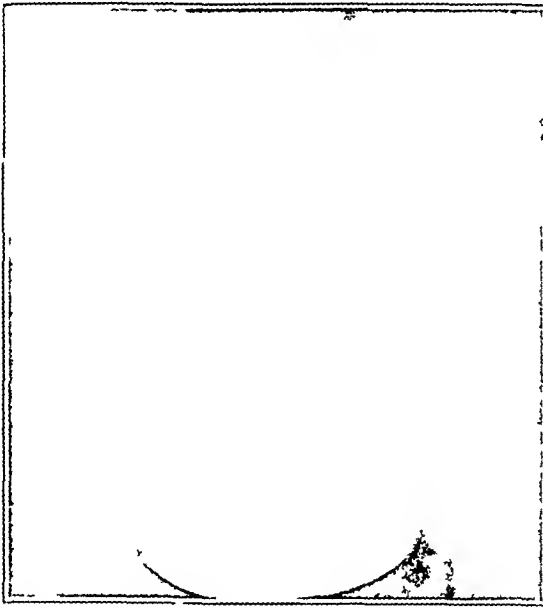


Fig 7—Photograph of patient whose roentgenograms are shown in figure 4. Note the lack of deformity and the type of healing.

CASE 8—W T, a man, aged 25, had tuberculosis for two years. He was well nourished and apparently a good risk. Roentgenograms showed many small cavities throughout the upper part of the left lung with fibrosis and a much thickened pleura. The right lung was clear. Following a first stage thoracoplasty on the lower five ribs, the patient had a stormy convalescence with distention, vomiting and an acute dilatation of the stomach. The second stage was delayed unusually long, and a phrenicotomy was done in the interval. For the first four days following the second stage he did well, then the pulse became weak, irregular and rapid, respiration labored and shallow, and he died on the fifth day. The cause of death was not ascertained.

CASE 9—S N, a woman, aged 34, was well nourished and a good risk. She had been ill with tuberculosis for two years. Roentgenograms showed much cavitation in the upper part of the left lung and a very thick pleura. There was a fibrosed area of healed tuberculosis in the upper part of the right lung. Following

a first stage thoracoplasty in which the lower five ribs were resected, a severe streptococcic infection of the wound developed. The wound was opened widely, and irrigated with a surgical solution of chlorinated soda (Dakin's solution), and a transfusion given. The patient improved, and a second transfusion was given two weeks after operation. Ten minutes after this was given, she died suddenly. The blood had been cross-agglutinated and was from the donor for her first transfusion. Autopsy failed to reveal a pulmonary embolism, and death seemed due to the transfusion as no other cause could be found.

SUMMARY

In a series of nine fatal cases, death was due to the operation in three, and in six it occurred some time afterward. Of the six patients who survived the operation and died later, two were extremely desperate risks and probably should never have been subjected to operation, two died of generalized tuberculosis and two died from extension of the disease to the good lung. Of the three whose deaths may be attributed to operation, one died of mediastinal flutter, one from transfusion and infected wound, and one of undetermined causes.

ACTINOMYCOSIS OF THE ABDOMEN

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Actinomycosis is a chronic disease caused by the fungus *Actinomyces bovis*. It is characterized by the formation of abscesses, sinuses, granulation tissue and brawny, leathery infiltration of the surrounding tissues. A positive diagnosis is made by demonstrating the sulphur granule or by demonstrating the actinomycotic lesion in tissue, microscopically. The microscopic picture of a typical granule may be described as a central mass of branching mycelia, radiating peripherally, and ending, usually, in clubs.

TABLE 1—Site of Primary Lesion in Sixty-Two Cases

Site	Cases	Per Cent
Appendix	48	77.5
Appendix, sigmoid	2	3.2
Appendix, diverticulum	1	1.6
Tonsil, appendix	1	1.6
Pelvis, appendix	2	3.2
Gallbladder, appendix	2	3.2
Sigmoid	1	1.6
Right groin	2	3.2
Right upper quadr.	2	3.2
Abdominal wall	1	1.6

* If the original site is questionable, the one listed first is considered the more likely.

I have been unable to substantiate or contradict the two current theories of the mode of infection: (1) that the organism is carried into the tissue by some foreign material like straw and (2) that the organism is already present in the mouth and that an injury, such as a straw is likely to cause, serves to provide a portal of entry. The source of the disease in this series was evident in only a few cases. The disease was considered abdominal in type when the abdominal wall or the abdominal viscera was involved. Thirty-six per cent of the patients were farmers.

The site of the lesion (table 1) in the intestinal tract was predominantly the ileocecal region. In forty-eight cases (77.5 per cent) the lesion was apparently primary in this region, whereas in eight other cases (13 per cent) it was questionably in this region.

It would seem reasonable to assume that the fungus may be caught and harbored at a point of stasis, such as at the ileocecal region, or

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in a diverticulum, from which it gains entry into the intestinal wall, as a result of injury to the mucosa. Frequently, there is secondary infection which results in formation of an abscess. It is probably at this stage that the patient first experiences symptoms.

In the abdominal type of actinomycosis, symptoms may be chronic or acute. In the chronic cases, there are seldom any symptoms and, in many instances, the presence of a mass in the right lower abdominal quadrant is the first indication of a lesion. Fever, malaise, pain and tenderness usually are concomitant with secondary bacterial invasion. In a high percentage of cases, this invasion occurs early in the course of the disease. The acute form, therefore, is much more frequently encountered than the chronic form. The great frequency with which the ileocecal region is involved, together with the early secondary bacterial invasion, explains the almost stereotyped group of symptoms which is encountered at the onset of the illness in the acute form.

The physician in attendance usually finds signs of acute appendicitis and advises operation. At operation, an appendical abscess frequently is found and amply drained. The appendix may or may not be removed, depending on the lesion and the condition of the patient. After the operation, the patient, in a high percentage of cases, will make an apparently normal convalescence, the wound will heal, in the case of a ruptured appendix, in from three to four weeks. Several weeks after operation, the patient begins to feel a little under par, he may have recurrence of fever, accompanied by chilly sensations, with a distinct chill at times, he feels weak and looks toxic. A region of tenderness is noted either in the incision or at some remote place such as in the flank or the right renal region. By this time, an abscess has formed. When this is drained, a sinus develops and discharges for an indefinite period. Since the nature of the disease is not recognized, every means is utilized to bring about healing and closure of this troublesome sinus. In most cases it does close, if only temporarily. In the meantime the fungus, by direct growth, progresses along the fascia, peritoneum and muscle fibers, possibly in the direction of least resistance, leaving in its wake leathery and brawny tissue, until, perhaps, some obstacle or resistance is reached and another abscess forms. Toxic symptoms recur and are relieved by drainage of the abscess and the formation of a sinus. In a similar manner, new abscesses and sinuses form while old ones may reopen, throughout the entire course of the disease. As the disease spreads by direct growth, involvement of the abdominal viscera and contiguous structures is rather extensive.

Late in the course of the disease, the blood stream may become infected and metastatic abscesses may be found in any part of the body. It is said that actinomycosis does not spread by way of the lymphatics except by direct growth. Complications (table 2) usually found are perinephric, nephric, hepatic, subphrenic and rectal abscesses, fecal



Fig 1—Actinomycotic node in omentum (hematoxylin and eosin, $\times 350$)

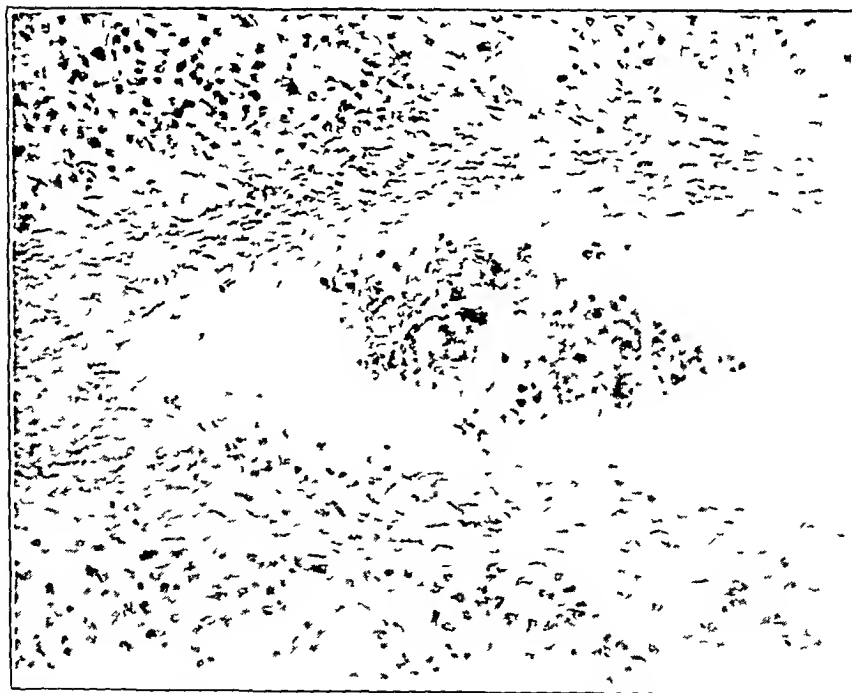


Fig 2—Actinomycotic abscess of the liver, thrombus of vessel is shown (hematoxylin and eosin, $\times 150$)

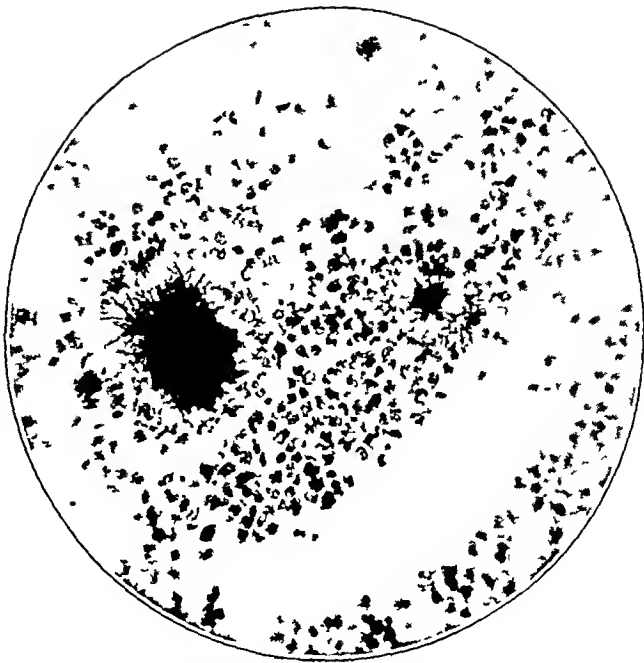


Fig 3—Typical actinomycotic lesion Mycelial threads and the indistinct outline of the clubs are shown (methyl violet, $\times 300$)

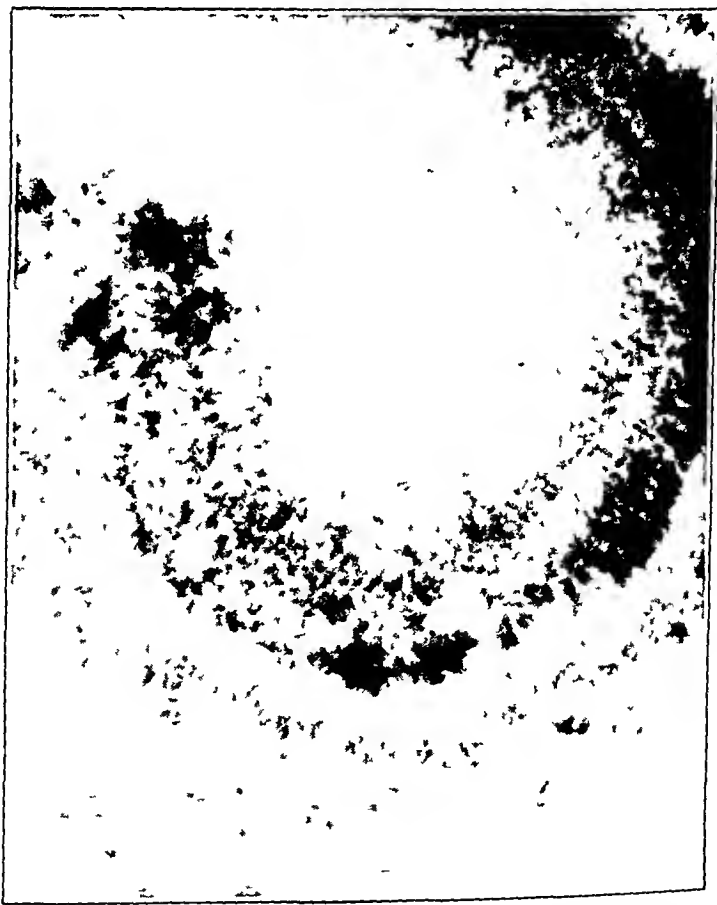


Fig 4—Actinomycotic lesion, clubs at the periphery of the lesion are shown (hematoxylin and eosin, $\times 550$)

fistula, infiltration of the psoas muscle, pelvic masses, and extension to the hip, groin and abdominal wall. The bladder was involved in three cases of the series observed, giving rise to dysuria, frequency and burning, and in one case, a vesical fistula had formed. The lung is secondarily involved in 25 per cent of the cases of abdominal actinomycosis. If the lesion is primary in the ileocecal region, the lung is affected in 20 per cent of the cases, if the lesion is primary in the upper part of the abdomen, the lung is affected in 50 per cent of the cases.

In treatment, it is especially important to instruct the patient to observe every precaution to prevent the spread of the disease, not only in his own body but to other persons.

Probably the greatest hope in the treatment of patients with abdominal actinomycosis lies in its early recognition, even then it is arrested with difficulty. Treatment used at the Mayo Clinic at present may

TABLE 2—*Structures Involved Secondarily in Sixty-Two Cases*

Structures	Cases
Lungs	15
Liver	11
Right renal	8
Pelvis	4
Abdominal wall	4
Right psoas	3
Groin	3
Bladder	3
Fecal fistula	3
Right hip	2
Rectal abscess	1
Rectal mass	1
Veins (phlebitis)	1
Scrotum	1
Iliac fossa	1
Spine	1

be surgical or medical or roentgen ray and radium may be employed. A combination of the methods is frequently used to advantage. Surgical methods are indicated for incision and drainage of abscesses, curettage of sinuses, and for the establishment of permanent drainage. In rare instances, radical operation has been effective. Medical treatment is directed to upbuilding of general health. The patient also is given massive doses of a saturated solution of potassium iodide, and the dosage is increased to the point of tolerance. Chitty has used tincture of iodine given in milk with good results. Application of roentgen ray and radium is a highly specialized form of treatment, and in the hands of competent men has given gratifying results.

Of sixty-two cases of actinomycosis of the abdomen that have been studied, twenty-nine patients have died, seven have not improved, six have improved, follow-up data could not be obtained concerning twelve, and the disease apparently has been arrested in eight.

Table 3 gives the date of onset, the duration of symptoms in terms of months both prior to registration and until death and the treatment received, in the twenty-nine cases in which death was caused

by actinomycosis The average duration of symptoms prior to registration was fifteen months The average duration of symptoms from onset of the disease to death was twenty-one months There were two

TABLE 3—Summary of Twenty-Nine Cases in Which Death Occurred

Case	Date of Onset	Duration of Symptoms Prior to Registration, Months	Duration of Symptoms to Death, Months	Treatment
1	5/25	6	13	Röntgen ray, radium potassium iodide
2	5/24	6	22	Radium, potassium iodide
3	3/16	8	10	Potassium iodide, neoarsphenamine
4	8/15	13	15	Drainage, roentgen ray, potassium iodide
5	1/16	6	7	Röntgen ray, radium, potassium iodide
6	1/17	12	12	General measures
7	1/20	7	12	Potassium iodide, roentgen ray
8	10/19	17	29	Potassium iodide, radium
9	4/19	24	26	Radium, roentgen ray, potassium iodide
10	12/24	3	7	Röntgen ray, potassium iodide
11	11/14	11	11	Potassium iodide, general
12	6/09	3	88	Röntgen ray, potassium iodide
13	6/17	3	7	Röntgen ray, radium, potassium iodide
14	11/16	11	1	General
15	3/16	1	2	Röntgen ray, potassium iodide
16	7/18	12	19	General, potassium iodide
17	3/23	6	9	Potassium iodide, copper sulphate
18	11/20	18	25	Röntgen ray, radium, potassium iodide
19	12/19	23	25	Röntgen ray, potassium iodide
20	2/26	0 5	5	Drainage of appendix, roentgen ray, potassium iodide
21	4/17	11	24	Aspiration, potassium iodide
22	5/22	11	13	Potassium iodide
23	3/22	7	10	Potassium iodide
24	11/22	11	24	Potassium iodide, roentgen ray
25	12/15	18	19	Potassium iodide
26	/06	180	211	Röntgen ray, potassium iodide
27	7/21	6	7	Potassium iodide
28	5/19	3 5	45	Potassium iodide
29	5/22	5	21	Potassium iodide
Average duration		15 3	21	

TABLE 4—Summary of Eight Cases Considered Arrested

Case	Date of Onset	Duration of Symptoms Prior to Registration, Months	Total Duration of Symptoms, Months	Disease Arrested, Months	Onset to Last Follow Up, Data, Months	Treatment
1	10/16	4	18	106	124	Sodium iodide intravenously, potassium iodide
2	6/17	4	17	96	113	Radical excision of colon and abdominal wall, roentgen ray and radium, potassium iodide
3	10/20	26	31	31	62	Röntgen ray, radium, potassium iodide
4	3/21	11	37	44	81	Röntgen ray, radium, potassium iodide
5	1/24	8	23	6	29	Röntgen ray, radium, potassium iodide
6	3/25	7	8	3	11	Röntgen ray, radium, potassium iodide
7	3/25	1	3	26	29	Incision of abdominal abscess, roentgen ray, radium, potassium iodide
8	4/25	11	14	30	44	Röntgen ray, potassium iodide

cases of long duration, cases 12 and 26, noted in table 4 If these cases are excluded, the average duration of symptoms from onset to registration would be nine months, and from onset to death fourteen and a

half months. The exact date of death could not be ascertained in three cases. These were excluded in making the computation of average duration of symptoms from onset to death. In nine of the cases (21 to 29 inclusive, table 4) the disease had extended to the lungs. If these are excluded, the average duration of symptoms from onset to registration is nine and a half months, and from onset to death, twenty and a half months.

There are eight cases in which the disease apparently has been arrested (table 4).

SUMMARY

The early symptoms of actinomycosis of the abdomen are those usually associated with acute appendicitis. Later, the disease is characterized by multiple abscesses and persistent sinuses, about which the tissue is leathery and brawny. The treatment consists in free drainage, the administration of potassium iodide, upbuilding of the general health and proper treatment by roentgen ray and radium. The course of the disease is usually chronic and the ultimate result is poor (figs 1 to 4).

TRAUMA TO THE INTESTINES

THE IMPORTANCE OF THE LOCAL LOSS OF FLUID IN THE PRODUCTION OF LOW BLOOD PRESSURE^{*}

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Of the different methods that have been employed in producing "shock" in experimental animals, probably the most frequently used has been that of trauma to the intestines. Mann¹ stated, "The easiest and most certain method of producing shock is by exposure and traumatization of the abdominal viscera. This, judging from the literature, has been the method used by nearly all investigators of shock." Several investigators have gone so far as to state that this is the only method by which shock can be produced experimentally. However, during the past ten years, the method of traumatizing large areas of skeletal muscle as described by Cannon and Bayliss² has been used probably with equal frequency.

It has been commonly believed by many that "shock," regardless of the method of its production, is associated with an accumulation of blood in the capacious splanchnic area. Wallace, Fraser and Drummond,³ in many operations on wounded men, did not find such to be the condition. They stated, "We would, therefore, state that in the course of many hundreds of abdominal operations undertaken upon patients in all degrees of traumatic shock we have not found any primary splanchnic congestion to exist." When the abdominal contents had been exposed to the atmosphere for a prolonged period or when an inflammatory process had become established, they found what they considered to be a secondary vascular dilatation. Many observers have commented on the congestion that occurs in the splanchnic area when the intestines are irritated. Morison and Hooker⁴ found that an isolated loop of gut that was wrapped loosely in rubber tissue gained in

* Submitted for publication, March 17, 1930

* From the Department of Surgery of Vanderbilt University

1 Mann, F. C. The Peripheral Origin of Surgical Shock, *Bull. Johns Hopkins Hosp.* **25** 205, 1914

2 Cannon and Bayliss. Note on Muscle Injury in Relation to Shock. Report of Shock Committee of the British Medical Research Committee, March, 1919, no 26, pp 19-23

3 Wallace, Cuthbert, Fraser, John, and Drummond, Hamilton. The Distribution of Blood in Traumatic Shock, *Lancet* **2** 727, 1917

4 Morison, R. A., and Hooker, D. R. The Vascular Tone and the Distribution of the Blood in Surgical Shock, *Am. J. Physiol.* **37** 86, 1915

weight in the terminal stages of shock. Mann¹ stated that the factors involved in the reaction of the intestines to irritation were the same as those involved in any other local inflammatory process, and that they did not involve the central nervous system to any greater extent. The observations of the Shock Committee of the British Medical Research Committee⁵ on traumatic shock supported the theory that shock is produced by histamine or a closely related substance that produces a general bodily effect.

The results of work reported in a previous communication⁶ indicate that the low blood pressure which results after trauma to an extremity of the experimental animal is due to the loss of blood into the traumatized area. These experiments did not include a determination of the results that are obtained many hours after mild trauma, but only the effects that are obtained in the first few hours after rather severe trauma. No evidence for the action of a histamine-like substance was obtained. The present study was undertaken in order to try to determine whether the low blood pressure that is produced by trauma to the intestines is due to agencies that exert a general bodily effect or whether it is due simply to local alterations in the traumatized area.

METHOD

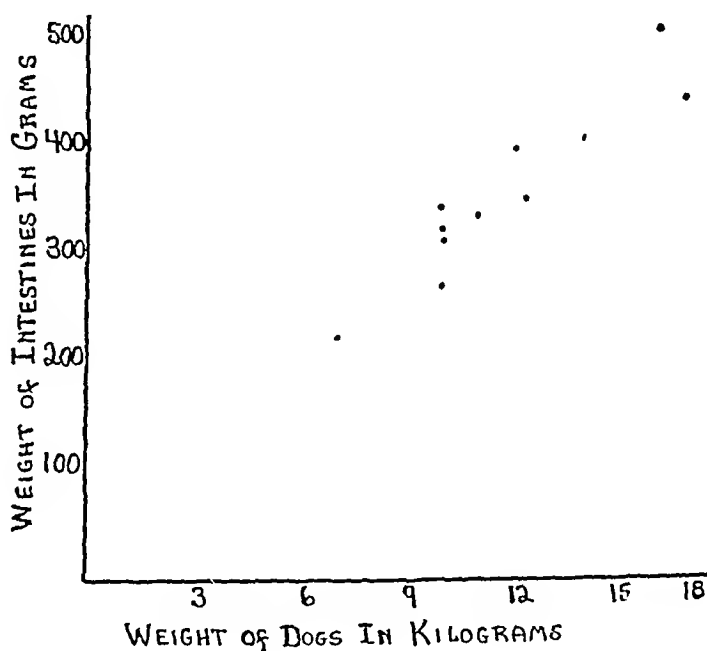
Dogs were used in all experiments. A sufficient amount of sodium barbital (0.3 Gm per kilogram of body weight) was given to keep the animal thoroughly anesthetized during the experiment. The level of the mean blood pressure was used as the criterion of the degree of shock. This was determined by placing in the carotid artery a cannula which was connected to a mercury manometer. The weight of the animal was determined accurately before the traumatization was begun. That part of the small intestine that is between Treitz ligament and the appendix was delivered through a midline abdominal incision. Gauze sponges of known weight were placed under the intestines in order to collect the fluid that escaped from the visceral peritoneum. The intestines were traumatized in ten of the twelve experiments by pinching them with the fingers. In the remaining two experiments, the trauma consisted of pulling repeatedly on the mesentery of the exposed intestines. The trauma was intermittent, the average total duration of the trauma in the different experiments being three hours and twenty-five minutes. When the gauze that was placed beneath the intestines became saturated with fluid, it was placed in a container that prevented evaporation and it was replaced by dry sponges. At the completion of the experiment, the sponges were again weighed, and the difference between the weights of the sponges at the beginning and at the termination of the traumatization was determined. After the decline in blood pressure that was desired had been produced, the dog was again weighed, and the loss in weight of the entire animal was determined. The part of the intestinal tract that had been traumatized was removed, after clamps had been

⁵ Reports of Shock Committee of the British Medical Research Committee, nos 25, 26 and 27, 1919. Published by His Majesty's Stationery Office, London.

⁶ Blalock, Alfred. Experimental Shock. The Cause of the Low Blood Pressure Produced by Muscle Injury, *Arch Surg* 20:959 (June) 1930.

placed across its pedicle. The weight of this was determined. The animals were not fed on the morning of the day of the experiments, and there were practically no feces in the small intestine.

In order to obtain an approximate idea of the weight of a similar portion of the intestinal tract when no trauma had been instituted, the weight of the intestines between Treitz' ligament and the appendix was determined in eleven dogs. These animals were anesthetized by barbital or ether. This portion of the intestines was removed immediately after opening the peritoneal cavity, and the weight was determined. From these figures and those for the weights of the dogs, the average weight of the intestinal tract per kilogram of body weight was determined. This average figure was multiplied by the weight of the dogs that were traumatized in order to gain an approximate idea as to what the intestines weighed before the trauma was instituted. The average weight of the intestines per kilogram of body



The weight of the excised intestine in eleven dogs in which no trauma was instituted. The weight of the intestines in grams is plotted against the weight of the dogs in kilograms.

weight in the control experiments was 30.7 Gm. The weights in individual experiments are shown in the chart.

The figure that was chosen as giving roughly the amount of available fluid that was lost from the circulating blood volume was obtained by adding the difference in the weight of the dog at the beginning and the end of the trauma to the difference between the determined weight of the traumatized intestine and the estimated weight of the nontraumatized intestine of a dog of the same weight. The sum of these figures divided by the weight of the dog gave the percentage of the body weight that was lost.

The hemoglobin of blood obtained from the femoral vein was determined before the trauma was begun and at its termination. After the intestines had been removed and weighed, they were placed in salt solution. They were incised in many places, and an attempt was made to wash out all of the blood that they contained. The amount of whole blood that was present in the washings was

obtained by multiplying the percentage of hemoglobin of the fluid by the total amount of the fluid and dividing by the percentage of hemoglobin of the whole blood. The amount of blood that had been collected by the sponges was determined in the same way.

RESULTS

The interval that elapsed between the initiation of the trauma and the reduction of the blood pressure to the desired level varied in the different experiments from three hours and ten minutes to eight hours. The mean blood pressure at the time that the trauma was discontinued varied from 26 to 68 mm of mercury. Trauma to the intestines resulted in a concentration of the blood as revealed by the determinations of hemoglobin. The average increase in the percentage of hemoglobin in all experiments was 38 per cent.

The sponges that were placed under the intestines in order to collect the secretions gained in weight from 125 to 520 Gm in the different experiments. This difference in weight of the sponges in most instances represented about one-half of the difference between the weight of the animal at the beginning and that at the termination of the trauma. This discrepancy is explained in part at least by the fact that part of the fluid evaporated from the surface of the intestines and from the sponges. The difference in the weight of the dog at the beginning and the end of the experiment varied in the different experiments from 195 to 690 Gm. This indicates that fluid lost from the body in the different experiments varied approximately from 195 to 690 cc. The average weight of the dogs was 12.18 Kg, and the average loss of fluid from each animal was 433 cc. A small part of this can be accounted for by that lost in the expired air. This is relatively unimportant, as it was found in control experiments that dogs weighing 12 Kg lose only about 60 Gm when observed for a period corresponding to the average duration of the experiments in which the intestines were traumatized. Precautions were observed in all experiments to guard against false values obtained by loss of urine or feces.

The weight of the traumatized intestine was greater than that of the estimated weight of the intestine before trauma by amounts varying from 11 to 233 Gm. In view of the fact that the weight of the normal intestine had to be computed from figures obtained on dogs other than those that were traumatized, the variations are not surprising. The average increase in weight of the intestines as computed was 103 Gm.

It was believed that the difference between the weight of the animal at the beginning and that at the termination of the trauma plus the difference between the weight of the traumatized intestine and its estimated normal weight would give an approximate idea as to the combined losses of fluid from the blood stream and the body tissues. This loss in the different experiments varied from 206 to 878 Gm and the

The Effects of Intestinal Trauma

Experiment	Con- trol Blood Pressure Before Amputation, Mm Hg	Time Between Initial Trauma and Amputation	Con- trol Hemo- globin, per Cent	Hemo- globin After Amputation, per Cent	Initial Weight of Sponges, Gm	Weight of Sponges Before Amputation, Gm	Difference in Weight of Sponges, Gm	Estimated Initial Weight of Intestines, Gm	Weight of Intestines at Amputation, Gm	Difference in Weight of Intestines, Gm	Control Weight of Dog, Kg	Weight of Dog Before Amputation, Kg	Difference in Weight of Dog, Gm	Loss of Weight in Dog Plus Gain in Weight of Intestine, Gm	Per centage of Body Weight	Blood From Intes- tine, Sponges, Cc	
1	103	5 hr 30 min	67	100	200	340	140	392	500	108	12.91	12.49	20	123	3.31	57	25
2	100	3 hr 15 min	80	130	180	340	160	172	575	103	15.39	15.1	290	393	2.55	99	13
3	104	3 hr 10 min	61	105	270	500	230	377	610	233	12.295	11.985	110	543	1.11	43	55
4	91	6 hr 50 min	?	96	200	455	255	271	405	134	8.83	8.115	115	519	0.22	70	93
5	138	3 hr 40 min	88	103	220	365	145	275	340	65	8.97	8.70	270	335	3.73	39	88
6	114	3 hr 30 min	96	108	225	350	125	334	345	11	10.895	10.70	195	206	1.89	17	41
7	120	5 hr 0 min	83	88	265	785	520	411	530	89	11.37	13.68	690	779	5.12	88	500
8	98	4 hr 20 min	55	100	275	650	375	485	575	90	15.805	15.26	545	635	4.02	38	26
9	113	6 hr 25 min	60	67	380	745	365	437	655	218	14.24	13.53	660	878	6.16	103	111
10	116	8 hr 0 min	60	82	270	450	180	292	320	28	9.52	9.08	440	468	1.92		
11*	90	4 hr 10 min	?	76	235	380	145	282	480	198	9.18	8.85	330	528	5.75	45	60
12*	112	6 hr 10 min	60	96	330	725	395	431	450	19	14.045	13.31	735	751	5.39	37	39

* Trauma consisted entirely of pulling on mesentery.

* Trauma consisted entirely of pulling on mesentery In all other experiments, it consisted of pinching intestines

average loss was 541 Gm. The loss in fluid expressed in percentages of body weight varied in the different experiments from 1.89 to 6.22 per cent, and the average loss was 4.48 per cent. In ten of the twelve experiments, the calculated loss represented more than 3 per cent of the body weight, and in eight of the twelve experiments, it represented more than 4 per cent. Determinations of the amount of whole blood that was present in the sponges showed that the red cells in most experiments constituted a relatively small proportion of the total loss. It was obviously impossible to recover all of the blood from the intestines, and hence no conclusion could be reached as to the relative parts played by plasma and red cells in the increase in weight.

The results that were obtained in all of the experiments on intestinal trauma are given in the accompanying table.

As has been stated previously, the intestine that was to be traumatized was pulled outside the peritoneal cavity through the incision in the anterior abdominal wall. It is interesting that although there was a copious loss of fluid from the intestine that was traumatized, there was no demonstrable loss of fluid from the organs that were left in the peritoneal cavity. Neither did these organs appear macroscopically to be engorged with blood. The walls of the gallbladder did not become edematous, and they retained their bluish color. In all experiments, the spleen decreased greatly in size during the traumatization. The weights were not determined, but the decrease was estimated at 50 per cent. In some instances, blood was found in the lumen of the large intestine at the completion of the experiment. The amount of this was not determined, and it was neglected in determining the fluids that were lost from the circulation.

In several additional experiments, the effects of passing a stream of compressed air over the exposed intestines were determined. The loss in weight from evaporation was rapid. The body temperature of the animal fell quickly, and usually death resulted before as much fluid had been lost as was found in the experiments in which the intestines were traumatized.

COMMENT

Prolonged trauma to the intestinal tract resulted in a decline in the blood pressure. Similar results were obtained regardless of whether the trauma consisted of pinching the intestines or of pulling on the mesentery. The decline in blood pressure was almost certainly due to a diminution in the circulatory blood volume, as the preponderance of evidence at the present time indicates that there is a vasoconstriction at least during the early stages of the shock. There are several possibilities as to the manner in which the blood volume was reduced: (1) hemorrhage outside the body or into the tissues, (2) loss of plasma

from the blood stream by filtration, with a concentration of the blood, and (3) stasis of blood in the traumatized area. External hemorrhage was measured with moderate accuracy by collecting all of the blood that was absorbed by the sponges. This constituted a small part of the total loss of fluid. The blood pressure was determined at infrequent intervals, and small cannulas were used, so that the amount of blood that was lost in the "washings" amounted to only a few cubic centimeters. There was a great loss of fluid from the blood stream by filtration, as determined by the increase in the weight of the sponges and by the difference in the weight of the animal at the beginning and the end of the experiment. The marked increase in the concentration of the blood in most experiments indicated a tremendous loss of plasma. Determinations of the hemoglobin indicated the minimum loss of blood through filtration of the plasma, as any local retention of the red cells would decrease the percentage of hemoglobin of the blood from the femoral vein. In several of the experiments, the large losses of fluid and the relatively small increase in the hemoglobin indicated that stasis was playing a detectable rôle in the diminution in the circulating blood volume. That there was stasis in the traumatized area is indicated by its weight being greater than that of the estimated normal. This observation is confirmatory of those of Morison and Hooker,⁴ who showed that an exposed and isolated loop of the intestine increased in weight in the terminal stages of shock.

Gasser, Erlanger and Meek⁷ determined the protein content of the plasma of the blood after clamping the aorta. They found that the protein content of the plasma underwent no marked change during the process of the concentration of the blood and believed that the plasma was lost mainly as a whole. In uncomplicated hemorrhage in small amounts, there is a passage of fluid from the tissue spaces into the blood stream. Starling⁸ explained this as being due to reduction of the blood pressure in the capillaries, so that the filtration pressure within them no longer effects the greater osmotic pressure of the plasma as compared with the lymph, and water passes into the blood stream. There is doubt whether or not water passes into the blood stream when a low blood pressure is produced by trauma. Cannon⁹ stated, "It is one of the unexplained features of shock that with a low venous and arterial pressures this process does not occur. Instead, the plasma as a whole makes its escape through the vessel walls." The fluid that escaped from the intestines in the present study was not analyzed. This

7 Gasser, H. S., Erlanger, Joseph, and Meek, W. J. *Studies in Secondary Traumatic Shock. IV. The Blood Volume Changes and the Effect of Gum Acacia on Their Development*, *Am J Physiol* **50** 31, 1919.

8 Starling. *Fluids of the Body*, Chicago, W. T. Keener & Company, 1909.

9 Cannon. *Traumatic Shock*, New York, D. Appleton & Company, 1923.

will form the subject of future study. In view of previous work, it seems most likely that the plasma made its escape as a whole. Possibly at the same time that plasma was being lost from the blood stream in the injured area, fluid was passing from the tissue spaces into the blood stream in the uninjured parts of the body. This exchange cannot continue indefinitely, since the available fluids in the body tissues are soon consumed. If the fluids that were lost from the surface of the visceral peritoneum in the present experiments consisted in the main of plasma, it is evident that there must have been a tremendous reduction in the circulating volume of blood. In a large series of dogs, Gasser, Erlanger and Meek⁷ found the average blood volume to be 97 per cent of the body weight. They estimated that the plasma constitutes 60 per cent of the volume of the blood. The calculated average loss in weight in the experiments with intestinal trauma was 4.48 per cent of the body weight. If it is assumed for the moment that all of the fluid that was lost was plasma and that it was not replaced by fluid from the tissues, it is to be seen that 77 per cent of the total plasma was lost. This is probably impossible, for in such a high concentration the red blood cells most likely would not circulate. It is likely, however, that the loss of plasma was sufficient to cause so much concentration of the blood that the internal friction of the corpuscles against the walls of the blood vessels was greatly increased. Concerning the effects of concentration of the blood, Cohnheim¹⁰ stated, "The concentration of the blood due to water inanition is evidently too slight to affect the heart and vessels to any considerable extent. As regards the withdrawal of water by artificially increasing the diffusion into the abdominal cavity, we know only that it may prove fatal to rabbits, but are ignorant of the effects of this condition when prolonged." He believed the effects of the concentration to be first and chiefly an enormous increase of the frictional resistance in the capillaries. Trevan¹¹ found that the internal friction rises rapidly when the concentration of the corpuscles is increasing. The stagnation of the blood that is caused by the concentration is accentuated by the decrease in arterial pressure that results from the loss of fluid from the blood stream.

It has been shown by Blalock and Harrison¹² that normal dogs usually reach a state of severe shock after blood amounting to from 3 to 4 per cent of the body weight has been removed. A comparison of the deleterious effects of the removal of equal amounts of whole

10 Cohnheim. Lectures in Pathology, London, The New Sydenham Society, vol 1, p 465, 1889

11 Trevan. Biochem J **12** 60, 1918

12 Blalock, A, and Harrison, T R. The Regulation of the Circulation. V The Effect of Anemia and Hemorrhage on the Cardiac Output of Dogs, Am J Physiol **80** 157, 1927

blood and of plasma has not been satisfactorily determined Kallius¹³ stated that the serum and not the red blood cells plays the more important rôle in the replacement of an acute loss of blood Abel, Rowntree and Turner¹⁴ found that it was possible to withdraw by repeated bleedings in a single day a volume of blood more than twice that contained in the body, with no apparent injury to the animal, if only the corpuscles suspended in Locke's solution were returned after each bleeding In the present experiments on intestinal trauma, there was no replacement of the fluid that was lost It seems likely that the loss of plasma from the blood stream amounting to 4 per cent of the body weight would produce an effect approximately as grave as the loss of the same amount of whole blood It has been stated that the calculated loss of fluid in eight of the twelve experiments amounted to more than 4 per cent of the body weight In these experiments, it is believed that the alterations in the traumatized area alone were sufficient to account for the reduction in the blood pressure The loss of fluid from and the accumulation of blood in the traumatized area result in a reduction in the blood pressure Operating to sustain this decrease in pressure are the increase in the viscosity of the blood, the elevation of the internal friction of the corpuscles against the walls of the vessels, the decrease in the amount of blood that returns to the heart and the decrease in the cardiac output Erlanger, Gesell and Gasser¹⁵ believed that the loss of fluid into and through the tissues of the bowel and the sequestration of blood in the intestinal capillaries and venules suggested a mechanism through which a reduction in blood volume might occur Excision of the stomach, spleen and intestines led them to believe that this was not the entire mechanism They stated, "But if this is the mechanism, the fact that after excision of the stomach, intestines, and spleen the arterial pressure falls almost exactly in the same way as after exposure of and manipulation of the intestines, and the fact that the changes in peripheral resistance are also alike, necessitate assuming that blood is thus removed from circulation, not alone in the parts of the body directly traumatized, but elsewhere also" In the three experiments that they performed, the animals were anesthetized by ether, and death followed the removal of the stomach, intestines and spleen at periods of time ranging from four and one half to seven hours These experiments do not prove that the decline in blood pressure following

13 Kallius, H W Experimentell Untersuchungen über die Wirkung des Serums bei der vitalen Bluttransfusion, *Deutsche Ztschr f Chir* **212** 289, 1928

14 Abel, Rowntree and Turner Plasma Removal with Return of Corpuscle- (Plasmapheresis), *J Pharmacol & Exper Therap* **5** 625, 1913-1914

15 Erlanger, Joseph, Gesell, Robert, and Gasser, H S Studies in Secondary Traumatic Shock I The Circulation in Shock after Abdominal Injuries, *Am J Physiol* **49**:90, 1919

traumatization of the intestines is due to factors other than the loss of fluid from and the accumulation of blood in the injured area. The removal of the stomach, intestines and spleen is necessarily associated with the removal of a considerable part of the total volume of blood. Although this is not followed in their experiments by an immediate decline in blood pressure, it almost certainly renders the animal more liable to a drop in pressure during prolonged ether anesthesia. They do not state whether or not the peritoneum was closed. If the peritoneum was left exposed to air, undoubtedly there was a considerable loss of fluid from it. Even if the incision was closed, there was probably a moderate amount of loss of fluid from the injured peritoneum. No mention is made as to the presence or absence of fluid in the peritoneal cavity at the time of death.

In two of the twelve experiments, the calculated loss of fluid from the blood stream amounted to less than 3 per cent of the body weight. In one of these, the mean blood pressure was still rather high (65 mm of mercury) at the time the experiment was terminated. The cause for the decline in pressure was undertermined. It seems unlikely that it was due entirely to the loss of fluid from the traumatized area. It is possible that it was due in these two exceptional experiments to the barbital, for it has been found in a large series of experiments that the giving of barbital without producing trauma is occasionally associated with a slow decline in the blood pressure.

The amount of fluid loss that can be tolerated without producing a marked decline in the blood pressure is probably influenced by several factors. In the experiments in which a stream of cool air was blown over the intestines, the temperature of the animal fell rapidly. Death was caused more quickly and with less loss of fluid than in the experiments in which the intestines were traumatized. Barbital seems to render the heat regulating mechanism of the body unstable, and possibly this was partially responsible for the difference.

Gasser, Erlanger and Meek⁷ studied shock produced by the injection of large doses of epinephrine hydrochloride, by occlusion of the aorta or vena cava and by exposure and manipulation of the intestines. As regards the effects of these procedures on the spleen, they stated, "The spleen is usually swollen and has dark raised areas which consist of hemorrhages into the pulp. This swelling and hemorrhage in some cases produce a spleen many times the normal size." These experiments were performed on dogs. Moore¹⁰ produced shock in various ways in cats and determined the size of the spleen. Ten experiments were performed. In six of these, shock was produced by crushing of

16 Moore, R. M. The Volume of the Spleen in Traumatic Shock, *Am J Physiol* 89 508, 1929

the thigh muscles and the testicles, in three, the peritoneum was opened, and the cavity was inflated with air for two hours at a pressure equal to 40 cc of water, and in the remaining experiment, the animal was cooled. After a low blood pressure had been produced by each of these procedures, the size of the spleen was found to be reduced. In regard to the condition of the splanchnic blood vessels in shock, he stated, "The close relationship which exists between the state of contraction of the spleen and that of the splanchnic vessels in general seems to justify the conclusion that in the experiments reported the splanchnic vasoconstrictor mechanism was operating powerfully and efficiently at a time when the blood pressure was below the critical level." Moore made the reservation that exposure or manipulation of the abdominal viscera leads to local congestion. This, he believed, is a local response to the trauma and is not due to a paralysis of the vasoconstrictor center. The size of the spleen was observed at the beginning and at the termination of the present experiments on dogs. In all instances there was a tremendous decrease as a result of the trauma. Apparently, the vessels of the traumatized intestine were dilated and those of the spleen were constricted. A vasoconstriction probably existed in that part of the intestinal tract that was not traumatized, as no engorgement with blood was apparent and there was no detectable weeping from the peritoneal surfaces.

It was found by Bradburn and Blalock¹⁷ that histamine, when injected in sufficient amounts to produce a sustained decrease in the blood pressure, caused edema of the wall of the gallbladder. In the present experiments, the gallbladder appeared entirely normal, indicating that histamine was not liberated in sufficient amounts from the traumatized area to account for the decline in pressure.

SUMMARY

The effects of trauma to the intestines have been studied in twelve dogs. The loss of fluid from the body and into the traumatized area of the intestines has been determined. This loss in eight of the twelve experiments amounted to more than 4 per cent of the body weight. The average loss in all experiments was 4.48 per cent of the body weight. Red blood cells constituted only a small part of the fluid that escaped from the peritoneum covering the intestines. Reasons are given for the belief that the loss of fluids from and into the traumatized area was the chief if not the sole cause for the reduction in the blood pressure.

¹⁷ Bradburn, H. B. and Blalock, A. Unpublished Observations on the Effects of Histamine on the Gall Bladder, 1929.

FORTY-THIRD REPORT OF PROGRESS IN ORTHOPEDIC SURGERY *

PHILIP D WILSON, M D

LLOYD T BROWN, M D

M N SMITH-PETERSEN, M D

JOHN G KUHNS, M D

AND

EDWIN F CAVE, M D

BOSTON

RALPH K GHORMLEY, M D

ROCHESTER, MINN

MURRAY S DANFORTH, M D

PROVIDENCE, R I

GEORGE PERKINS

LONDON, ENGLAND

ARTHUR VAN DESSEL, M D

LOUVAIN, BELGIUM

AND

C HERMANN BUCHOLZ, M D

HALLE, GERMANY

CONGENITAL DEFORMITIES

Congenital Clubfoot—Brockman,¹ in the Robert Jones prize essay, advocated the correction of rigid and relapsed types of clubfoot by an open operation, based on the conception that the deformity was due primarily to a congenital atresia of the socket for the head of the astragalus. The operation aimed at making this socket sufficiently large for the head of the astragalus to be replaced in its normal position, and in addition the muscles, which controlled the variations in the capacity of the socket, were lengthened. Under an Esmarch bandage an incision was made on the outer side of the foot over the os calcis. Through this the plantar muscles and fascia were detached as far backward and inward as possible. A second incision was made on the inner side of the foot, and the remaining attachments of these muscles were completely freed from their origin. The origins of the abductor hallucis from the sheaths of the tendons and the vessels passing into the sole of the foot were dis-

* This Report of Progress is based on a review of 206 articles selected from 469 titles dealing with orthopedic surgery appearing in the medical literature between May 1, 1930, and Sept 15, 1930. Only those papers that seem to represent progress have been selected for review.

¹ Brockman, E P. *Congenital Club-Foot (Talipes Equinovarus)*, Bristol, John Wright & Sons, 1930.

sected off. The tendon of the tibialis posticus was then identified. If this prevents the calcaneoscaphoid joint from being identified, it should be detached from the tubercle of the scaphoid and, if necessary, its accessory attachments going to the other bones of the tarsus divided. The next step was to dissect the structures off the inferior surface of the tarsal bones until the whole of the inferior and internal surfaces of the scaphoid and the inner aspect of the sustentaculum tali were exposed. All the ligaments on the inner and inferior aspects of the calcaneoscaphoid joint were then divided. It was then possible to restore the forefoot to its normal position in relation to the astragalus. The foot was not put up in full correction, owing to possible interference with the circulation. At the end of fourteen days, under another anesthetic, full correction was obtained by forcible manipulation and the tendo achillis elongated, if a true equinus was present. After from six to eight weeks in plaster ordinary boots were supplied, a clubfoot shoe ordered to be worn at night, and reeducation of the evertor muscles was commenced. The author did not favor operating on patients under the age of 3, because of the large amount of fat and the smallness of the structures in the sole.

[ED NOTE—We do not feel that the whole deformity of clubfoot can be so easily described. Any one who has studied Hoke's collection of astragali must have been impressed by the extreme and varied types of deformities they presented, particularly in respect to the head and neck. These must be taken into account in the correction of clubfoot deformity. Except that the author recommends a second incision along the outer border of the os calcis, we see little fundamental difference between this operation and that of Ober.² We prefer gentle manipulative methods of correction under the age of 3 or 4 years.]

Congenital Dislocation of the Hip—Jaeger³ made a plea for early recognition of congenital dislocation of the hip and described his method of treating the condition when discovered in infancy. He employed a hip splint of rustless steel which was fastened to the pelvis and chest by circular bands and to the foot and ankle by a leather anklet and foot piece. Lateral compression of the head into the acetabulum was obtained by an adjustable pad fastened to the splint and placed directly over the trochanter. By gradually abducting the thigh the head of the femur was gently pressed into the acetabulum. The splint was worn continuously for from four to eight months.

Beck⁴ reported the late results of 107 cases of old congenital dislocation of the hip in Bier's surgical clinic in Berlin. In all cases reduc-

2 Ober, F. B. An Operation for Congenital Equinovarus Deformity. Preliminary Report, J. A. M. A. 65:621 (Aug. 14) 1915.

3 Jaeger, C. H. Surg. Gynec. Obst. 50:757 (April) 1930.

4 Beck, Heinz. Zentralbl. f. Chir. 56:2582, 1930.

tion was done at or after the sixth year. The method was the typical reduction over the upper rim of the acetabulum after previous traction with wire on the lower end of the femur in order to bring the head down to the height of the acetabulum. The fixation in plaster cast was carried out for from three to six months, but not longer because of the danger of permanent fixation. After the ninth year the reduction did not succeed, except by several forced manipulations under ether. On the whole, the results had not been very good, even when the primary result was satisfactory, the end-result was not completely successful on account of the insufficient formation of the acetabular shelf. In ten cases a fracture resulted, in eight cases a solid ankylosis and in eight cases redislocation. At the age of from 12 to 15 years typical symptoms appeared in many cases of successful reduction caused by the secondary deformations of the head.

Syndactylism—Davis and German⁵ studied the cases of fifty patients with syndactylism treated at the Johns Hopkins Hospital. Eighteen per cent of the patients gave a family history of syndactylism. They were treated by skin flaps, whole thickness skin grafts and occasional plastic operations on the bones of the fingers. The authors advised against extensive plastic operations at an early age, they said that only that which was necessary to prevent disturbance in growth and increasing deformity in infancy, should be done and that the operative procedures should be completed at the age of 6 or 7.

Bifid Os Calcis—Sever⁶ reported three cases of bifid os calcis in infants. He was unable to find any reference to this in the literature. The condition was bilateral and might be mistaken for fracture. The defect usually disappeared at or before the age of 3 years.

Experiments on Embryo—Debrunner⁷ did experiments on the embryos of dogs and rabbits during intra-uterine life. These experiments showed that fetal tissue had very slight resistance against mechanical insults. Even a loose constriction of a leg with a thin silk strand led to a deformity resembling amniotic amputation. On the other hand, embryonic tissue had a marked power of regeneration, as an osteotomy of a long bone healed within four days. Parts of the extremities amputated by constriction were never found after birth showing the marked resorptive power of the intra-uterine fluid.

METABOLIC DISTURBANCES OF BONE

Osteitis Fibrosa—In most cases Eliason and North⁸ regarded trauma as the cause of osteitis fibrosa. They were inclined to belittle

5 Davis, J. S., and German, W. J. Syndactylism (Coherence of Fingers or Toes), Arch Surg **21** 32 (July) 1930.

6 Sever, J. W. Surg Gynec Obst **50** 1012 (June) 1930.

7 Debrunner, H. Arch f Orthop **28** 25, 1930.

8 Eliason, E. L., and North, J. P. Ann Surg **91** 833 (June) 1930.

the infectious theory advocated by Phemister. The common locations for the lesion were pointed out as the greater tuberosity of the humerus, lower end of the radius, one or the other end of the tibia and the femur near the greater trochanter. These they stated were regions frequently exposed to trauma. For treatment they favored a combination of the roentgen rays and surgical intervention, realizing that prolonged roentgen treatment might damage the adjacent growing epiphysis, and that recurrences might follow operative treatment alone. It was essential to observe such patients over a period of several years after any form of treatment.

Osteomalacia—Gargill and his associates⁹ reported metabolic studies in a case of osteomalacia occurring in an American woman, aged 38. The patient was first placed on a diet low in calcium and vitamins, on which a normal person gave a negative calcium balance of 67 mg. On this diet the patient gave a negative calcium balance of 45 mg. She was given 50 cc. of a physiologically tested brand of cod liver oil and 200 Gm. of powdered skimmed milk, but no improvement was noted. Oscodol tablets (concentrated cod liver oil) were then added, and slight improvement occurred. The addition of treatment with ultraviolet light still further improved the condition. With the addition of large amounts of calcium in the form of calcium lactate, phosphorus in the form of disodium acid phosphate and a diet rich in vitamins, improvement was observed. The pain over the ribs and back, which had been the chief symptom, wholly disappeared, and progressive recalcification was observed in the roentgenograms. The authors reviewed the literature. In this case they felt that they were dealing with a form of adult rickets without any evidence of an endocrine disturbance.

Compere¹⁰ noted the frequent association of osteomalacia and allied disorders with hyperparathyroidism. A case of osteomalacia was reported in which marked improvement occurred after removal of a parathyroid tumor. Eleven additional cases were reported from the literature. In eight of these there were tumors of one of the parathyroid glands demonstrated at operation. In five of these there was symptomatic improvement and increased deposit of calcium after removal of the tumors.

Renal Rickets—Schoenthal and Burpee¹¹ reported in detail a case of renal rickets in a child of 8 years, and gave the complete metabolic studies carried out over a period of five years. According to the authors,

9 Gargill, S. L., Gilligan, D. R., and Blumgart, H. L. *Metabolism and Treatment of Osteomalacia. Its Relation to Rickets*, Arch. Int. Med. 45: 879 (June) 1930.

10 Compere, E. L. *Surg. Gynec. Obst.* 50: 783, 1930.

11 Schoenthal, L., and Burpee, C. *Renal Rickets*, Am. J. Dis. Child. 39: 517 (March) 1930.

two types of renal rickets might be distinguished (1) that due to congenital malformation of the kidney or urinary tract, and (2) another type due to chronic renal insufficiency, chronic interstitial nephritis becoming manifest in later childhood. The renal insufficiency led to an acidosis which was supposed to cause mobilization of calcium from the bone resulting in decalcification.

Zanoli¹² reported two observations of his own, and collected from the literature thirty-two more cases of what he was pleased to call renal pseudorickets. The syndrome consisted of a renal lesion, skeletal deformities, especially genu valgum, and retardation of development of the body. In studying the cases, he found that in the majority the retardation of development began either at birth or in early infancy. The appearance of skeletal deformities was variable. Rarely it occurred in the first or second year of life, more often at 4 or 5 years, sometimes at 7 or 8 years and not infrequently at from 12 to 15 years. It occurred more commonly in boys than in girls. Skeletal deformities constituted one of the cardinal symptoms, being present in 67 per cent, and the most common deformity was genu valgum, often bilateral. In the great majority of cases, the renal condition was chronic interstitial nephritis. The retardation of development in stature was such that the child was from two to nine years behind other children of the same age, with an average of three or four years. Correction of deformities should be undertaken with care, as the children are poor operative risks.

[ED NOTE—The term renal pseudorachitism seems to us a more suitable name than renal rickets or the term recently suggested in an editorial of the *Journal of the American Medical Association*¹³ "renal infantilism." Fortunately, the condition hardly seems common enough in this country to cause much concern over the nomenclature.]

GROWTH DISTURBANCES OF BONE

Effect of Roentgen Radiation—Desjardins¹⁴ reported a case of small round cell sarcoma of the humerus in a child in which roentgen treatment was followed by an inhibition in the growth of the right humerus and feeble development of the muscles about the right shoulder. The patient was followed up for a period of four and a half years. A continued repair of the humerus was noted, but the muscle and bone remained much smaller than the corresponding parts of the opposite side. The author reviewed the literature on retardation of growth by the roentgen rays.

12 Zanoli, R. *Chir d org di movimento* **14** 539 (March) 1930.

13 Renal Rickets—An Undesirable Designation? Editorial, *J A M A* **95** 116 (July 12) 1930.

14 Desjardins A U. *Radiology* **14** 296, 1930.

ANATOMIC STUDIES—BACK AND FOOT STRAIN

Pain in the Lower Part of the Back—Brackett¹⁵ divided derangements of the lower part of the back into cases with normal anatomic structure and those with anatomic malformations. In cases with normal anatomic structure, rest and fixation during convalescence were all that was required in the way of treatment. In cases with structural abnormality, the physician had to determine to what extent the abnormality interfered with the functional integrity of the lumbosacral and sacro-iliac joint, and the treatment had to be modified accordingly. The author felt that sacralization of the fifth lumbar vertebra played very little part in derangements of the lower part of the back. A horizontally placed sacrum and irregular lumbosacral articulations were potential factors in back strain, particularly because of the strain they produced on the sacro-iliac joints.

Riches¹⁶ made a study of the end-results in 75 of 113 patients with pain in the lower part of the back, who had been treated by mobilization of the back under general anesthesia. He found the following results:

	Number	Number Improved	Per Cent
Chronic back strain	30	26	87
Sacro-iliac strain	25	23	92
Lumbosacral strain	3	1	33
Spinal arthritis	13	6	46
Neurotic spine	4	0	0

No patient was classified as improved unless he had returned to work and did not suffer more than occasional pain in the back after over-exertion. After-treatment, with exercises with the intention of maintaining the mobility produced while under anesthesia, was essential. The manipulation sometimes needed repeating twice or even three times. Cases with a traumatic history gave better results (97 per cent improved) than those with an insidious, nontraumatic onset. Sixty-eight per cent of the cases classified as strain (chronic pain in the back, sacro-iliac or lumbosacral) were traumatic in origin. Roentgenograms in the cases of strain were negative, except for anatomic anomalies which appeared to be of no consequence. Stereoscopic roentgenograms in cases of spinal arthritis showed tipping of the bodies and of the articular processes sometimes. In cases designated "chronic back strain" the lesion was over a wide area, being usually a strain of the erector spinae muscles or of ligaments underlying the muscles, diagnosed clinically by tenderness over the erector spinae, spasm of the muscles and limitation of lateral flexion of the spine toward the opposite side. In cases designated "sacro-iliac strain" the history was a sudden unguarded movement giving rise to sharp pain referred to one or the other sacro-iliac joint.

15 Brackett, E. G. *J. Bone & Joint Surg.* **12**: 325, 1930.

16 Riches, E. W. *Lancet* **1**: 957 (May 3) 1930.

This was followed by a sense of insecurity. On examination there was tenderness localized to the posterior superior spine or just below. Straight knee hip flexion caused pain to be felt in the sacro-iliac joint. In cases designated "lumbosacral strain," the tenderness was localized accurately to the lumbosacral junction in the midline or just to either side of it. Flexion of the spine was free and painless, but hyperextension was painful. In cases designated "spinal arthritis" all movements of the lumbar spine were limited by muscular spasm.

Riches concluded: 1. In chronic back strain and sacro-iliac strain manipulation was successful in 90 per cent of the cases, and when there was evidence of a definite exciting trauma, success might be anticipated in almost all cases. 2. Cases of lumbosacral strain were not permanently improved by manipulation. 3. Improvement in 50 per cent of cases of spinal arthritis might be expected. 4. Cases of neurotic spine did not respond to manipulation. 5. Efficient after-treatment was necessary.

[ED. NOTE—It is to be regretted that Riches did not have a control group of patients which was given "efficient after-treatment" without the manipulation. We question whether he would not have found a high percentage of cures by this method alone.]

Auxiliary Organs of the Spine—Schanz¹⁷ pointed out the importance of the aorta and the abdominal organs as auxiliary organs for the support of the spine. The aorta was filled with a rather thickish fluid under the marked pressure of 150 mm. of mercury. Thus it represented a column which supports the spinal column on the left side. Perhaps this was one reason why the dorsal spine more often showed a curve to the right side than to the left. The intestinal organs, filled to some extent with air and supported by the abdominal muscles, supported the spine in heavy lifting by their pneumatic powers.

[ED. NOTE—Schanz' theory is interesting. The influence of such mechanical factors as the one mentioned is too little considered by orthopedists.]

Communications Between Knee and Tibiofibular Joints—Weeks¹⁸ made twelve dissections of knees and found that the tibiofibular and knee joints communicated in about 15 per cent of cases. The author was led to this by two cases of acute suppurative arthritis of the knee following resection of the upper end of the fibula for painful and infected amputation stumps. He felt that this observation supplied the explanation.

Development of the Bone—Zweibel¹⁹ described an elaborate process of depigmentation and staining of an embryo. A fetus of from 10 to 12

17 Schanz, A. Arch f. klin. Chir. 159:624, 1930.

18 Weeks, C. Am. J. Surg. 8:798, 1930.

19 Zweibel, L. Am. J. Surg. 8:517, 1930.

weeks required about three months, and the time was progressively longer with increase in the age of the fetus. In the completed specimen the entire bony skeletal system was visible, and cartilage could be differentiated from bone, the bone taking on a red opaque color and the cartilage a brownish, translucent, hyaline-like appearance. The bones of the skull especially were brought out distinctly. The ossification centers were easily traced and studied, and a truer conception of the gross differences between cartilaginous and membranous bones was had from these stained specimens than could be obtained from the finest roentgenograms.

The basis for development of the two types of bony tissue was embryonic connective tissue. In one type of development cartilage preceded the bone, and in the other membrane formation preceded the bone. In intramembranous ossification the calcium salts were deposited in the ordinary embryonic connective tissue. In intracartilaginous ossification, hyaline cartilage first developed in the same general shape as the future bone and the calcium salts were afterwards deposited within the mass of the cartilage. The membrane bones, for example, many of the flat bones of the skull and face, were ossified by bundles of connective tissue fibers becoming impregnated with calcium salts. These calcified bundles were calcification centers. These bundles were clearly demonstrated, especially in the younger of the stained specimens. In each of these areas, the cells increased in number, the tissue became vascular, and some of the cells became more oval with a distinct nucleus and considerable cytoplasm, they then arranged themselves in single, fairly regular rows along the bundles of calcified fibers as osteoblasts. Under the influence of the osteoblasts, a thin layer of calcium was deposited between the osteoblasts and the calcified fibers. In this way true bone was formed. On the inner surface of newly formed bone, osteoclasts caused dissolution, while new bone was being formed on the outer surface, especially under the periosteum, where the osteoblasts were numerous, this caused growth and enlargement of the bone.

Intracartilaginous ossification, physiologically, was similar, except for the fact that it was performed by cartilage, shaped similarly to the future bone. The center of ossification was usually single in these bones (the sternum was one exception, having several such centers). This center was in the center of the bone, especially in the long bones, and the osteogenic tissue pushed in both directions toward the end of the cartilage (in long bones toward the epiphysis).

Summarizing, ossification in cartilage consisted of the following stages: (1) multiplication of cartilage cells, (2) calcification of the cartilage, (3) absorption of the calcified cartilage and (4) deposition of true bone.

ANTERIOR POLIOMYELITIS

Immune Serum—Fairbrother²⁰ claimed to have obtained an anterior poliomyelitis serum from the horse after injecting emulsions of spinal cords of monkeys that had died of poliomyelitis. This serum appeared to be as potent as human convalescent serum. This important experimental work was being continued.

Rise in Temperature Preceding Appearance of Symptoms in Experimental Poliomyelitis—Kramer and his co-workers²¹ found a rise in temperature of from 2 to 3 degrees in monkeys that had been inoculated with poliomyelitis virus, from one to three days before the onset of the usual recognizable symptoms. This rise in temperature was associated with changes in the spinal fluid. The authors felt that this rise in temperature marked the onset of a stage in the experimentally produced disease corresponding to the preparalytic stage in infection in human beings.

[ED. NOTE—Experimental workers in poliomyelitis continue to uncover interesting facts in connection with its spread and mode of entrance into the body. Both of the foregoing papers offer new and interesting sidelights on the problem.]

TUBERCULOSIS

Tuberculous Arthritis of the Hip—McMurray²² found that of 310 patients with tuberculosis of the hip (the diagnosis being made clinically), 26 died while undergoing treatment in the hospital. Of 53 patients who had ceased all treatment for five years or more, 23 had bony ankylosis and 30 fibrous ankylosis with a range of movement varying between half normal to none. A sinus had been present in every patient who had obtained a bony ankylosis, and although in a few cases the sinus still discharged, the patient had a painless joint and good function. Seven of the 30 patients with fibrous ankylosis had had osteotomy performed to correct deformity, and in 2 patients a second osteotomy had proved necessary. Six of the 30 patients with fibrous ankylosis made no complaint, and in the five years that had elapsed since the cessation of treatment there had not been any tendency toward deformity or a recurrence of the arthritis. McMurray concluded that even in the absence of bony ankylosis, if the hip was kept in a position of abduction for a sufficiently long period there was no reason why the joint should not become sound, and the patient capable of carrying on even heavy work. He agreed, however, that when there was a tendency

20 Fairbrother, R. W. Brit J Exper Path **11** 43 (Feb.) 1930.

21 Kramer, S. D., Hendric, K. H., and Aycok, W. L. J Exper Med **51** 933, 1930.

22 McMurray, T. P. Liverpool Med-Chir J **38** 82, 1930.

to deformity in adduction, arthrodesis of the joint was justifiable "at the end of treatment when the disease was cured"

The Bone-Graft Operation for Tuberculosis of the Spine—Albee²³ reported the results of twenty years' experience with his bone graft operation on 865 patients with tuberculosis of the spine. In 90 per cent of the cases the patients had been able to do hard work, such as heavy lifting and scrubbing, or to indulge in riding, tennis and swimming. In a few there were mild complaints of fatigue after the day's work or of occasional distress in the back. In the cases classed as good, there was still some mild reminder of the disease, but there was no noteworthy incapacity. In the cases in which the patient was as strong and active as if he had never been ill, the result was classified as excellent. In 69 cases, 8 per cent, the result was classified as fair since the patient complained of moderate pain at times or was not able to do more than light work or to indulge in active exercises without restrictions. Seventeen patients died, 3 during convalescence.

[ED. NOTE—Albee's figures cover a large group of patients and deserve to be studied carefully. The percentage of favorable results is higher than that of many other careful students who have previously reported, and the mortality rate in later years is much less than one would expect to find.]

PYOGENIC INFECTIONS

Osteomyelitis of the Spine—Steindler²⁴ presented a report on twelve cases of osteomyelitis of the spine, six being acute and six chronic. The patients with acute cases were all under 17 years of age. The ages of those with chronic cases ranged from 19 to 47 years. In the acute cases the lesion occurred in the vertebral body. *Staphylococcus aureus* was found in all of the acute cases in which the type of organism was determined. The most frequent sites for acute osteomyelitis were the twelfth dorsal and lumbar vertebrae, and wedge formation of the vertebra and kyphosis were the rule. In the chronic cases the lesions were more widely scattered. The diagnosis in either type was difficult. Abscess formation was common in the acute form. These abscesses frequently entered the spinal canal, producing pachymeningitis or compression of the cord. The prognosis was grave in the acute form, in which the mortality was 46 per cent. Most of the patients with the chronic form recovered, but convalescence was slow. Treatment in the acute form was surgical drainage of the abscess cavity. In the chronic form, recumbency and rest followed by support of the back were the best treatment.

²³ Albee, F. H. Bone-Graft Operation for Tuberculosis of the Spine, J. A. M. A. **94** 1467 (Mar 10) 1930.

²⁴ Steindler, A. I. Iowa M. Soc. **20** 246, 1930.

Use of Bacteriophage Filtrates in the Treatment for Suppurative Conditions—Rice²⁵ reported approximately 90 per cent of excellent results in 300 patients with suppurative lesions who were treated with bacteriophage filtrates. Among these cases were abscesses, carbuncles, boils, osteomyelitis, suppurative arthritis, cellulitis and bed-sores. The bacteriophage filtrate was at first specific for the bacteria involved, but later most of the patients were treated with a stock bacteriophage filtrate containing staphylococci and *B coli* bacteriophage. The bacteriophage was applied either by injection into the abscess cavity or by application as a wet dressing. The results were least good in osteomyelitis and in tuberculous sinuses secondarily infected. In these the author felt that the bacteriophage came in less close contact with the infection. The author reviewed the theories of the action of bacteriophage, but felt that an adequate explanation of the phenomena had not yet been given.

[ED NOTE—The use of bacteriophage has been advocated from time to time over a period of five years or more. Reports have varied from extreme optimism to total failure. Until such reports become more consistently favorable, we must regard this form of treatment as highly experimental.]

CHRONIC ARTHRITIS

The Prevention of Deformities in Chronic Arthritis—Swaim and Kuhns,²⁶ in an article on the prevention of deformities in chronic arthritis, said that deformities occurring in the lower extremities were important because they hindered or prevented walking. As they modified the patient's outlook and disturbed his mental well-being, they were probably more important than deformities in other parts of the body. Deformities should be anticipated and preventive measures applied early.

When deformity had developed, the authors emphasized the importance of gentleness in the procedure undertaken to correct it. Correction could be attempted by physical therapy and exercises during the day and plaster splints worn at night. These splints were made with the limb in as nearly a correct position as possible without discomfort. The plaster splints could be changed at frequent intervals as more correction was obtained. Rapid correction or manipulation under anesthesia while the disease was active led only to disaster.

Bacteriologic Studies—Margolis and Dorsey²⁷ studied the bacteriology of the epiphyseal marrow and of the joint structures in twenty-five cases of chronic infectious arthritis and in forty control cases. Fifteen specimens of epiphyseal marrow gave positive cultures in seven

25 Rice, T. B. *Am J M Sc* **179** 345, 1930.

26 Swaim, L. T., and Kuhns, J. G. *Prevention of Deformities in Chronic Arthritis Lower Extremity*, *J A M A* **94** 1743 (May 31) 1930.

27 Margolis, H. M., and Dorsey, A. H. E. *Chronic Arthritis Bacteriology of the Affected Tissues*, *Arch Int Med* **46** 121 (July) 1930.

All the synovial fluids were sterile. The organisms recovered in the control cases were looked on as contaminants or invaders. Five of eight rabbits given intravenous injections of cultures from the arthritic cases developed nonpurulent effusions of the joints. Streptococci culturally and morphologically the same as those injected were recovered from the tissues of the joints in six rabbits. Diphtheroid bacilli recovered from arthritic cases were injected into two rabbits. Arthritis did not develop in these rabbits.

[ED. NOTE—With all the careful bacteriologic investigations of chronic arthritis that are being made, we ought soon to be in a position to determine whether or not it is of infectious origin. A certain relationship to streptococcal infection appears to have been shown, but that it is due to direct bacterial invasion in every instance has not been proved.]

CIRCULATORY DISTURBANCES

Blocking the Sympathetic Nerves with Procaine Hydrochloride—White²⁸ developed a diagnostic test which he tried in twenty-four cases to determine beforehand the effect of sympathetic ganglionectomy. By blocking the sympathetic fibers to the arm or leg with procaine hydrochloride, he produced all the effects of ganglionectomy for a period of from two to four hours in a given extremity. Its use in selecting cases for ganglionectomy seems indicated.

NEUROLOGIC DISTURBANCES

Spasmodic Torticollis—The operation for treatment for spasmodic torticollis preferred by Frazier²⁹ consisted of intradural division or crushing of the posterior nerve roots bearing the afferent fibers from the particular muscles affected. In addition, the spinal accessory nerve on the affected side had to be divided. In his hands this technic had given better results than the extradural division of the cervical nerves at their points of exit from the spinal canal. He stated that it was extremely difficult to differentiate between torticollis with and without an organic basis, and as a rule the treatment was the same. So far as possible, an accurate estimate of the particular muscles involved should be made and division of the dorsal root nerves from these muscles performed.

An operative procedure for the treatment for spasmodic torticollis was reported by Dandy³⁰. A cervical laminectomy was performed fol-

28 White, J. C. Diagnostic Blocking of the Sympathetic Nerves to the Extremities with Procaine. Test to Evaluate the Benefit of Sympathetic Ganglionectomy, *J. A. M. A.* **94** 1382 (May 3) 1930.

29 Frazier, C. H. *Ann. Surg.* **91** 848, 1930.

30 Dandy, W. E. Operation for Treatment of Spasmodic Torticollis, *Arch. Surg.* **20** 1021 (June) 1930.

lowed by an intraspinal resection of the sensory and motor roots of the first three cervical nerves. The spinal accessory nerves were cut at their exit from the foramen magnum. This operation was performed on eight patients, of whom five were relieved and two improved, the remaining patient died of pneumonia three weeks after operation. The author believed that spasmodic torticollis was always organic in origin and that it was never restricted to a single muscle or group of muscles.

[Ed. NOTE—Some of the editors have observed the complete symptomatic relief for over a year of three patients with spasmodic torticollis by the use of rest and of orthopedic measures to decrease the hyperextension of the cervical spine.]

Neuritis—Wollman³¹ reported five cases of ulnar pressure neuritis and four cases of pressure neuritis of the common peroneal nerve developing in patients who had been bedridden for some time. He pointed out the importance of careful handling of such cases from the nursing standpoint to avoid pressure on these easily damaged nerves.

Localization of Tumors of the Cord—Elsberg and Cramer³² were opposed to the indiscriminate use of iodized oil in the localization of tumors of the cord, because they had observed patients who suffered from severe root pains and had vesical disturbances for a number of days after injections of iodized oil. They believed that multiple lumbar punctures carried out at different levels of the cord were much safer, and, though perhaps more tedious, were just as accurate as the injection of iodized oil.

TUMORS

Diffuse Osteoplastic Carcinomatosis of the Skeleton Due to Clinically Unrecognized Primary Carcinoma of the Prostate—Putti and Faldini³³ reported a case of osteoplastic carcinomatosis of the skeleton from primary carcinoma of the prostate, clinically unrecognizable. They considered the case worthy of note because: 1. It helped to confirm an idea worthy of dissemination, namely, that diffuse malignant tumors of the skeleton might be metastases from primary tumors that could not be recognized clinically. 2. The case was studied extensively, both while the patient was living and post mortem.

In arriving at a diagnosis, they stated that diffuse carcinomatosis of the skeleton from a tumor not possible to localize was most probably from the prostate, also, a diffuse tumor growth in a segment of the skeleton involving the entire area from the proximal to the distal epiph-

31 Wollman, H. W. *Am J M Sc* **179** 528, 1930.

32 Elsberg, C. A., and Cramer, F. *Multiple Lumbar Punctures: Their Value for Localization and Diagnosis of Tumors of the Cauda Equina*, *Arch Neurol & Psychiat* **23** 775 (April) 1930.

33 Putti, V., and Faldini, G. *Chir d org di movimento* **14** 505 (March) 1930.

ysis of the bone and not sparing the bone derived either from fibrous tissue or from cartilage was most likely to be a metastatic tumor

MISCELLANEOUS

Diagnosis of Lesion of the Shoulder—Meyer³⁴ discussed the roentgen diagnosis of lesions about the shoulder joint. He stated that the films usually failed to show any sign of gross damage, but that nevertheless certain minor changes were of considerable importance. He considered that the following signs pointed toward the presence of arthritis, the demonstration of atrophy of the bone, increased density at the lateral border of the greater tuberosity, a deepened furrow between the greater tuberosity and the head, hypertrophy of the lower border of the articular cavity, lessening of the width of the articular gap and the presence of irregular bony shadows in the capsule. He considered the intertubercular sulcus of particular importance.

[ED. NOTE.—We feel that some of the signs mentioned by the author are indicative of rupture of the supraspinatus tendon, and that arthritis when present under such conditions is quite likely to be of secondary origin. The characteristic appearance of this lesion consists of atrophy in the region of the greater tuberosity, increased density at the superior and lateral border, filling up of the intertubercular sulcus and the presence of irregular bony shadows in the capsule. Rupture of the supraspinatus tendon is often not recognized, and this leads to a confusion of the clinical picture with that of arthritis.]

Epicondylitis Humeri—Hansson and Horwich³⁵ reported a study of sixteen patients with "tennis elbow." They did not accept the theory of Osgood that the condition was due to an inflammation of the radio-humeral bursa, in spite of the two cases of cure by removal of the bursa which he reported. They agreed with Holmann, and stated that their conception of the pathologic condition in epicondylitis humeri, or tennis elbow, was that of a periosteal fracture with a myofascitis of the extensor muscles which originated from the epicondyle. Studies of the anatomy and physiology of the elbow and forearm, together with their knowledge of the phylogenesis and locus minoris resistens of muscles, and their clinical experience pointed to such a pathologic conception.

The condition existed in two forms: (1) the acute form, as seen in tennis elbow, and (2) the chronic form, which was usually occupational. The pathologic change was probably periosteal avulsion with a myofascitis. In real tennis elbow the periosteal symptoms predominated, while in the occupational type the myositis was worse. No treatment was of any avail unless the extensor muscles from the external condyle were relaxed. The best splint for this purpose was the cock-up splint.

³⁴ Meyer, H. *Chirurg* 2 241, 1930.

³⁵ Hansson, K. G., and Horwich, I. D. *Epicondylitis Humeri*, *J. A. M. A.* 94 1557 (May 17) 1930.

[ED NOTE—We consider it not improbable that two different types of pathologic change may be responsible for the clinical symptoms of tennis elbow. The conception of Hansson and Horiwich may explain certain cases, but that radiohumeral bursitis may account for other cases has been proved by the operative experience of some of the editors.]

Foreign Bodies in the Elbow Joint (Baseball Pitchers' Elbow)—Baseball pitchers' elbow was the name applied by Kirby³⁶ to a condition which was found in four patients in whom there was a fracture of the posterior inner surface of the head of the radius with the production of a loose body. The size of the bodies varied from that of a coffee bean to that of an almond. They consisted of cartilage, and, when sectioned, were found to contain bone in the center. The loose body was removed by an operation in all four patients, and all secured a fully useful joint with an arm and forearm as strong as before injury. All of the patients were baseball pitchers, and the injury consisted in a sudden, sharp pain while pitching.

Snapping Knee—Nat³⁷ reported the case of a man who while kicking a football felt something give way in his knee, and who ever since had complained that the knee gave an audible click on full extension.

On the outer side of the knee in front of the tendon of the biceps the iliotibial band could be made to slip backward and forward over the normal surface of the lateral condyle, immobilizing this band by pressing it against the condyle caused the click to disappear.

At operation, Nat found a tear of the deep fascia which filled the triangular interval between the tendon of the biceps femoris and the iliotibial band. This was repaired with complete relief from all symptoms.

A New Sign of Injury to the Semilunar Cartilage of the Knee—The difficulty of exact differential diagnosis in certain cases of internal derangement of the knee was emphasized by Bragard,³⁸ and he pointed out that the movements of the cartilage in different positions of flexion and extension of the knee might be used to determine the kind of lesion. In a case in which the medial cartilage was torn loose, local tenderness was produced by inward rotation, with the knee both in extension and in flexion, whereas in flexion with outward rotation the tenderness disappeared. The severity of the lesion was expressed by the slowness of the disappearance of pain when the knee was brought from the extended to the flexed position. Lesions of the lateral cartilage caused corresponding symptoms. On the other hand, with lesions of the capsule the pain was made worse by increasing the angle of flexion.

36 Kirby, F. J. *Foreign Bodies in the Elbow Joint "Baseball Pitchers' Elbow,"* J. A. M. A. 95:404 (Aug. 9) 1930.

37 Nat, B. S. *Lancet* 1:749 (April 5) 1930.

38 Bragard, K. *Munchen med. Wchnschr.* 77:682, 1930.

Chondromatosis of the Joint Capsule—Thirteen cases of chondromatosis of the joint capsule were studied by Kartal³⁹ He stated that there were two theories as to the cause of the condition (1) the tumor theory and (2) the theory of chronic irritation of normal cartilage islands of the synovia In the differential diagnosis, osteochondritis dissecans, arthritis, calcareous bursitis, hemophilic joints and myositis ossificans had to be considered The condition might be present for years without giving symptoms until an injury precipitated pain The author did not advise operative treatment unless the symptoms demanded it

Improved Air Injection Apparatus for Inflation of Joints—An improved apparatus for the inflation of joints by air has been developed by Berg⁴⁰ The author claimed for it the advantages that it allowed for complete aseptic aspiration of the diseased joint and provided an absolutely aseptic method of inflating a joint with sterile air at the desired pressure The apparatus consisted of a manometer, a sterilizing chamber and a pressure bulb, all being mounted on a small, detachable metal table

[ED NOTE—The inflation of joints with air has been practiced rather indiscriminately and with poor technic Several unfortunate accidents resulting from this procedure have come to the attention of some of the editors There is a place for the procedure, but it should be done carefully, and an apparatus such as that described by Berg will undoubtedly prove useful]

Etiology of Calcaneal Spurs—One hundred consecutive cases of exostosis of the os calcis observed at the Mayo Clinic were reviewed by von Lackum and Palomeque⁴¹ with the purpose of ascertaining how frequently the gonococcus was a factor in causing the condition Eighty-five of the patients were men and fifteen women In 44 per cent of the patients a history of gonorrhea was obtained, and in 56 per cent this history was lacking

The writers came to the conclusion that neither syphilis nor gonorrhea was a gross factor in the etiology Foci of infection in the teeth, tonsils or prostate gland, and possibly other obscure areas, particularly those bearing streptococci, probably played an important rôle in cases in which multiple etiologic factors were present The term "gonorrheal spurs" was a misnomer, and ought not to be used

BONE, JOINT AND TENDON SURGERY

The Use of Sodium Iso-Amyl-Ethyl-Barbiturate in Anesthesia—Experience is accumulating in the use of sodium iso-amyl-ethyl-barbiturate as an intravenous anesthetic and hypnotic, and reports on the results

39 Kartal, S T Surg Gynec Obst 51 99, 1930

40 Berg, R F Am J Surg 8 1277 (June) 1930

41 von Lackum, W H, and Palomeque, E J Gonorrheal Spurs a Misnomer, J A M A 95 472 (Aug 16) 1930

are beginning to appear. Mason and Baker⁴² employed the drug in 195 patients, and discussed the details of dosage and the methods of administration. Preliminary medication with morphine and atropine was the rule, and generally the drug was supplemented by some form of inhalation anesthesia. Frequently it was combined with spinal anesthesia. After the administration of sodium iso-amyl-ethyl-barbiturate, the patient went to sleep, the frequent preoperative anxiety was obviated, and much less inhalation anesthesia was required. There were certain disadvantages at times, such as delirium and pulmonary edema. The authors felt that when an operation was to be done, there was no contraindication to the drug except in extreme shock, diabetes, anemia or respiratory obstruction.

Brown⁴³ stated that he and his associates had employed sodium iso-amyl-ethyl-barbiturate as an intravenous anesthetic in eighty-two surgical cases. The following procedure was used. Either the night before the operation or early in the morning the patient was given 10 grains (0.65 Gm) of chlorotone, one-half hour before operation he received $\frac{1}{6}$ grain (0.01 Gm) of morphine and $\frac{1}{120}$ grain (0.0038 Gm) of atropine hypodermically. Sodium iso-amyl-ethyl-barbiturate was given in the dosage of 1 decigram per 10 pounds (4.5 Kg) of body weight intravenously at the rate of from 0.75 to 1 cc per minute. In most instances there was an initial fall in blood pressure of from 10 to 70 mm depending on whether the initial pressure was average or high. They observed that following the use of the drug postoperative gas pains were lessened. About twenty-five of their patients required catheterization. Special nursing was required in all cases for from twenty-four to forty-eight hours after operation.

Postoperative Shock and Shocklike Conditions. Treatment by Infusion in Large Volume—As a means of combating surgical shock, McFee and Baldrige⁴⁴ stated that they had used a method of intravenous infusion of saline in large volume administered slowly over a long time with benefit. They observed no untoward effects such as cardiac failure or pulmonary edema with amounts varying from 2,000 to 8,000 cc. The average amount given their patients was 4,500 cc. The solution had to be given slowly, and the rate of 1,000 cc per hour seemed satisfactory. They reported statistics and case histories which indicated that the method was beneficial.

Causes of Death After Operation—Neuhof and Aufses⁴⁵ made an analysis of the causes of death after operation, basing their figures on 800 consecutive autopsies performed at Mount Sinai Hospital and two

42 Mason, J. T., and Baker, J. W. *Surg. Gynec. Obst.* **50** 828 (May) 1930.

43 Brown, R. *Ann. Surg.* **91** 492 (April) 1930.

44 McFee, W. F., and Baldrige, R. R. *Ann. Surg.* **91** 329 (March) 1930.

45 Neuhof, H., and Aufses, A. H. *Ann. Surg.* **91** 321 (March) 1930.

other New York hospitals. Suppuration following operation for non-suppurating lesions was found to be an extremely common cause of death, 25.5 per cent. Forty-two per cent of the patients died as a result of the original disease, while pneumonia was found to be the cause of death in only 8 per cent. Suppurative complications after operations for nonsuppurative conditions were often unrecognized before death. The authors felt that the number of deaths from suppuration was in no way due to faulty technic, but depended on lowered resistance of the individual tissues.

Treatment for Snapping Thumb—Ottendorff⁴⁶ recommended the following method for the treatment for snapping or trigger thumb, at least for such cases as were due to thickening of the tendon sheath. Under local anesthesia a tiny, narrow-bladed knife was introduced subcutaneously into the tendon sheath, and the constricted or tight part of the sheath was divided in a longitudinal direction, the results of the operation could be controlled by active flexion and extension of the thumb by the patient, and the operation ought not to be considered complete until the tendon moved without obstruction. Following the operation, early and frequently repeated movements of the tendon were necessary to prevent the formation of adhesions.

Flexor Plasty of the Thumb to Overcome Thenar Palsy—Further experience had convinced Steindler⁴⁷ that the operation for thenar palsy which he first described in 1919 was an effective procedure. He had performed the operation twenty-three times, with fifteen successful results. Six patients obtained results that were considered fair, while in two the operation resulted in failure. The procedure depended for its success on the presence of a strong flexor tendon of the thumb. The long flexor tendon was split longitudinally from the level of the phalangeal joint to a point one-half inch (1.27 cm.) proximal to the metacarpophalangeal articulation. The radial half of the tendon was divided at the distal end, passed subcutaneously over the dorsum of the basal phalanx and sutured through a second incision to the dorsum of the thumb, or the tendon could be passed through a drill hole in the phalanx. It was necessary to splint the thumb in a position of adduction and flexion for a period of three weeks after operation, at which time exercises could be started.

Rupture of Tendons of the Hand—The classification of Hauck was followed by Mason⁴⁸ in studying rupture of the tendons of the hand. The types of rupture were (1) those due to direct trauma, (2) those due to indirect trauma and (3) spontaneous ruptures due to disease. For treatment for the subcutaneous rupture of the extensor tendon of

46 Ottendorff. *Zentralbl. f. Chir.* 57:1273, 1930.

47 Steindler, A. *Surg. Gynec. Obst.* 50:1005, 1930.

48 Mason, M. L. *Surg. Gynec. Obst.* 50:611 (March) 1930.

the finger at its insertion into the distal phalanx, he recommended the use of an aluminum splint holding the distal phalanx in hyperextension to be worn for a period of from six to eight weeks. Occasionally, even with this treatment the tendon might heal in a lengthened condition. For correction of this a step cut incision was made in the tendon, and the ends were overlapped. Damage to the joint capsule, if present, could be repaired at the same time. Rupture of the dorsal aponeurosis over the proximal interphalangeal joint required operative treatment followed by the use of a hyperextension splint for a period of four weeks. Although rare, dorsal dislocation of the tendons over the metacarpophalangeal joints could occur, and was occasionally congenital. In the early traumatic cases, splinting in extension might restore function, but in the long-standing cases operative treatment was required. Rupture of the tendons at the wrist usually occurred only after some disease, usually tuberculosis. Rupture of the flexor tendons was rare, and followed sudden extension of a tightly flexed finger. Operative treatment was usually necessary.

Reconstruction Surgery in Paralytic Deformities of the Foot—In discussing reconstruction surgery in deformities of the foot and leg resulting from poliomyelitis, Dunn⁴⁹ stated that before proceeding to operation every effort should be made to overcome the deformity by gradual stretching methods. Division of muscles for the correction of deformity should be avoided, as it weakens the muscles so that they function less well and are less valuable for transplantation. Transplantation of tendons ought to be restricted to the group with which they normally act. Transplanted muscles usually do not work well even after training, if made to work with a normally opposing group of muscles. In the severe types of paralyzes of the foot, arthrodesis of the tarsal joint ought to be performed preliminary to tendon transplantation or tenodesis.

From a study of the end-results of 109 stabilizing operations on the feet, Buzby⁵⁰ came to the following conclusion. Stabilizing operations should rarely be done before the age of 7. Lack of bony fusion was due to operation at too early an age, to insufficient removal of cartilage to nonapposition of denuded bone surfaces or to the use of the foot before there was solid bony fusion. Tendon transplants alone were not satisfactory, tending to become stretched out and functionless in a short time. The few indications for astragalectomy could be met equally well by a less mutilating operation, such as transverse tarsectomy with backward displacement of the foot.

[ED NOTE—The editors agree with most of the conclusions of Dunn and Buzby. They do not agree that transplantation of a tendon

49 Dunn, N. I. *Bone & Joint Surg.* 12:299, 1930.

50 Buzby, B. F. *I. M. Soc. New Jersey* 27:316, 1930.

to perform the work of an opposing muscle is always useless. Good results can be obtained almost as a routine from the transplantation of the peronei muscles to the dorsum of the foot and similarly, the biceps muscle may be transplanted to become an extensor of the knee. In the case of the foot, however, one should not ask too much of the transplanted muscles, and the best results are to be obtained after preliminary stabilization operations, nor do we believe that astriagalectomy has been entirely superseded by subastriagal or tarsal stabilization. We believe that this operation still has a place, although a very restricted one in the treatment for deformities of the foot.]

Bone-Block Operation for Drop-Foot—Campbell⁵¹ reviewed the results in 225 patients with paralytic feet on whom he had performed the bone-block operation for drop-foot which he had previously described. Excellent results were obtained in 92.8 per cent of the children and in 96.5 per cent of the adults. The paralytic equinus deformity had recurred in only 14 patients, and in 10 this result was ascribed to a defective operative production of a bony block at the posterior margin of the ankle joint. In the other 4 the recurrence was due to extreme relaxation of all the ligaments and soft structures about the ankle joint. In no case was there persistent pain from pressure on the new osseous process and in no instance was evidence of osteo-arthritis found.

Results of Operation for Hallux Valgus—The end-results of 219 operations for bunion performed on 135 patients at Stendler's Clinic were studied by Barnard.⁵² The types of bunions were classified as paralytic, static and arthritic. The operative procedures employed were the Mayo-Heuter, the Silver and the Porter. In a few patients a simple excision of the exostosis had been done. It was found that the end-results were considerably poorer at the end of a year than shortly after operation. Poor results constituted less than 10 per cent which argued strongly in favor of the operation. The Mayo-Heuter and Silver operations seemed to be the more satisfactory over the longer periods.

FRACTURES

Reduction of Fractures Under Local Anesthesia—Hempel⁵³ recommended the use of local and plexus anesthesia in the reduction of fresh fractures and felt that the method had so many advantages over general anesthesia that it ought to be in more general use. In fractures of the lower extremity he had found blocking of the lumbosacral and sciatic plexuses valuable especially as it could be done without changing the patient's position from the dorsal decubitus. He had found the method

51 Campbell W. C. *J. Bone & Joint Surg.* **12**: 317, 1930.

52 Barnard L. *Ann. Surg.* **91**: 937 (June) 1930.

53 Hempel C. *Zentralbl. f. Chir.* **57**: 519, 1930.

particularly useful in the reduction of dislocations, and without assistance had been able to reduce dislocations of the hips in adults

An Efficient Traction Apparatus for the Reduction of Fractures—Soutter⁵⁴ believed that the reduction of fractures of the long bones and also of many of the dislocations could be accomplished with relative ease if the muscles were first relaxed by traction and countertraction. He had devised a simple apparatus by means of which this could be accomplished without the necessity of employing one of the complicated fracture tables. The apparatus consisted of a rod of tubular steel about 80 inches long with a right angle bend at one end. The rod was made up of several sections each about 20 inches long. Each tube fastened solidly to the adjoining tube so that the rod could be built up to any desired length. Webbing straps were provided to attach to the extremities to serve for traction and countertraction. Traction was secured by means of two double block pulleys with a heavy cord, and a spring balance was provided that measured up to 100 pounds in order that a known amount of traction could be used. Traction in any amount up to 100 pounds could be obtained. When a steady traction force was applied for a certain time, the muscles became paralyzed, and the relaxation lasted for a definite interval after the traction force had been released. This gave the opportunity for gentle manual manipulation and reduction.

[ED NOTE—Some of the editors are acquainted with the author's traction apparatus and can testify to its mechanical efficiency. It can be adapted to almost any position of the extremity, and in addition has the advantage of being portable and of occupying a small space.]

Fractures of the Pelvis—A study was made by McNealy and Willems⁵⁵ of thirty-three cases of fracture of the pelvis. These injuries were caused by severe trauma, such as automobile accidents and crushing injuries. There had apparently been an increasing incidence of fractures of the pelvis in the last few years. The region most commonly involved was the pubis. Treatment should follow conservative lines unless definite operative indications presented themselves. Injuries of the urethra and bladder were the most common complications. Surgical shock frequently accompanied these fractures, and ought to receive immediate and primary consideration. Taken as a whole, these fractures offered a favorable prognosis, as to both life and function. In the group of patients studied the greatest number of days of treatment before final discharge was 305 and the least 35, the average being 95.

54 Soutter, R. Reduction of Fractures and Dislocations of the Long Bones. Apparatus for Obtaining General Relaxation of the Soft Parts, J. A. M. A. 94:1547 (May 17) 1930.

55 McNealy, R. W. and Willems, J. D. Am. J. Surg. 8:573, 1930.

Fractures of the Os Calcis—Simon and Stultz⁵⁶ advocated early operative treatment in all compression fractures of the os calcis. They found it possible to elevate the thalamus on superior portion of the lateral calcaneal surface underlying the superior articular facet, and they preferred a reconstruction operation of this type to subastragalar arthrodesis in the majority of cases. When the subastragalar joint had been considerably damaged, arthrodesis preceded by as much reconstruction of the os calcis as possible was the treatment of choice. Rarely was astragalectomy necessary.

Hermann⁵⁷ described the method of treatment which he had employed in eighty patients with fractures of the os calcis. The treatment was a modification of the method advocated by Cotton in 1908. It consisted in brief of molding the fragments into as nearly perfect position as possible, particular care being taken not to allow bone to pile up under the external malleolus. A small caliper tongs was next inserted into the posterior portion of the body of the os calcis. The heel was pulled down and the arch restored. The tongs were then removed, and sterile dressings and felt pad applied over the wound, while the foot was held in correct position a plaster boot was applied, the foot being fixed in a position of inversion and plantar flexion. The plaster casing was changed at the end of ten days, lateral pressure on the os calcis being maintained. Active exercises were started at the end of eight weeks, and weight bearing was permitted at the end of twelve weeks.

[ED. NOTE—The treatment for recent fractures of the os calcis seems still to be a debatable problem. The continuous traction method is not without danger. The method of reduction by remodeling is uncertain. Subastragalar arthrodesis is not always indicated. The reconstruction operation described by Simon and Stultz would seem of doubtful value. Hermann's article is impressive with a large number of successful end-results. In the old cases with persistent pain we feel that subastragalar arthrodesis is indicated, and that this operation is capable of relieving the symptoms.]

Fractures of the Astragalus—In writing on the subject of fractures of the astragalus, Sawyer⁵⁸ stated that they were caused by a force transmitted upward through the phalanges and metatarsals and not from a fall on the heel, as in the case of fractures of the os calcis. Fractures of the astragalus were frequently impacted. Operative treatment was rarely indicated, manipulative reduction and immobilization usually being sufficient to insure good results. It was necessary to resort to operative treatment when the fracture extended into the ankle joint.

56 Simon R and Stultz, E. *Ann Surg* 91 731 (May) 1930

57 Hermann O J. *New England J Med* 202 705 (April 10) 1930

58 Sawyer F J. *New England J Med* 202 629 (March 27) 1930

or if the impaction was so great that the contour of the bone was destroyed. Astragalectomy and open realignment of the fractures were the procedures of choice.

DISLOCATIONS

Cervical Dislocations—Brookes⁵⁹ advocated early manual reduction for dislocation of the cervical spine by the method of retrolateral flexion with rotation as described by Walton in 1904. The reduction was followed by prolonged immobilization in plaster. The author reported six cases in which the method had been used, which he added to the ten cases he had previously reported.

Dislocation of the Carpal Scaphoid—Higgs⁶⁰ reported two cases of dislocation of the carpal scaphoid reduced successfully by open operation ten and four weeks respectively, after injury. In each instance the traumatism had been produced by a fall from a motor cycle. The immediate results following operation were excellent. The later results were not recorded.

AMPUTATIONS

Optimum Sites for Amputation—Surgeons and limb fitters recently met at the Royal Society of Medicine in London⁶¹ to discuss the practical value of various amputation sites. Their conclusions were as follows. In the lower limb only two sites were recommended: below the knee, with 7 inches (17.78 cm) of tibia; and above the knee, with from 10 to 12 inches (25.4 to 30.4 cm) of femur. Symes' amputation was condemned because its average life was only about ten years after which time reamputation had to be performed for the comfort of the patient. The long thigh stumps had likewise failed to prove their staying qualities and their number was being gradually reduced by reamputation. In the upper limb only two sites were recommended: below the elbow, with from 6 to 7 inches (15.24 to 17.78 cm) of ulna; and above the elbow, with 7 or 8 inches (17.78 or 20.32 cm) of humerus, i.e., at least 2 inches (5 cm) above the epicondyles. Kineplastic amputations had proved failures because a satisfactory mechanical hand had not been evolved. Reamputation had been necessary in most of the thirty patients on whom kineplastic amputations had been performed in England.

Changes Incidental to Healing Bone in Amputation Stumps—Barber⁶² made a study of the changes in the ends of the bone in amputation stumps at intervals of from six days to years after operation. In

⁵⁹ Brookes T. P. J. *Missouri M. A.* **27** 177 (April) 1930.

⁶⁰ Higgs S. J. *Proc. Roy. Soc. Med. (Sect. Surg.)* **23** 1337 (Feb.) 1930.

⁶¹ Page C. M. and Verrall P. J. *Proc. Roy. Soc. Med. (Sect. Surg.)* **23** 1307 (April) 1930.

⁶² Barber C. G. J. *Bone & Joint Surg.* **12** 353 1930.

six days the sectioned end of the bone showed increased vascularity and rarefaction. At the end of thirteen days, the saw marks had been entirely obliterated by erosion, and a fairly well developed periosteal and endosteal callus was seen. When the bone had been sectioned in the spongy portion, the end of the bone was found well healed in fifteen days, and presented the waxy texture seen in old amputation stumps. When the amputation passed through the medullary cavity in the diaphysis, several weeks were required for the closure of the cavity by endosteal callus. After this period, the vascular channels in the end of the bone rapidly close, and the new bone assumes a waxy texture.

[ED. NOTE—The changes in the healing of bone in amputation stumps must vary depending on the technic used in treating the ends of the bones. The points that are most important to know are whether the aperiosteal, the periosteal or the osteoplastic method yields the best results, and which one is least likely to be followed by osteophytic formation.]

Suspension of Artificial Leg—Karfel⁶³ had seen many patients in whom trouble referable to the spine began to develop when they had been wearing artificial limbs for a certain period after amputation of the thigh. These patients often complained of pain located in the stump, and many of them had been subjected to reamputations for supposed neuromas or sensitive or improper scars, without relief. Careful examination showed the stump to be in good condition, but there was evidence of weakness and irritation in the spine. There was a marked increase of lumbar lordosis, the spinal muscles were often in a state of spasm, and points of tenderness could be demonstrated in various regions. The author thought that there was an evident connection between these symptoms and the improper mechanics induced by the use of the artificial limb and particularly by the habit of suspending it by a strap from one shoulder. Mechanically and physiologically, it was better to fix the artificial leg to the pelvis instead of hanging it from the shoulder, and patients in whom he had made this change experienced immediate relief from their former symptoms. Occasionally, it was necessary to connect the pelvic support with two shoulder straps, but these should be applied without tension. In resistant cases it might be necessary to substitute for the ordinary limb a limb made of light metal or to use a light pylon temporarily.

RESEARCH

Studies of Viosterol and Vitamin D—Bills and Wirick⁶⁴ gave graduated overdoses of viosterol to rats for more than seven months

63 Karfel, G. *Munchen med Wchnschr* 77 1356 1930

64 Bills I. C. E., and Wirick A. M. *J Biol Chem* 86 117, 1930

They found that the administration of viosterol in amounts 100 times the antirachitic dose had no effect on the general appearance, growth, reproduction or resistance to respiratory infections. Viosterol in doses 1,000 times the antirachitic dose was perceptibly harmful. Amounts 4,000 times the antirachitic dose were definitely injurious, and amounts 40,000 times the antirachitic dose were strongly toxic, the animals all dying within two months.

Hess and his co-workers⁶⁵ reported that in the course of a test of a large number of infants it was found that although viosterol, in its present dosage, conferred protection against rickets, some evidences of this disorder were apparent in a small number of cases. No hypercalcemia or other untoward symptoms developed. The cases that showed signs of mild rickets were remarkable for the fact that the inorganic phosphorus of the blood was maintained at its normal concentration, in no instance did the phosphorus fall below the normal level. This peculiar manifestation—rickets associated with undiminished inorganic phosphorus—had been noted previously when irradiated milk had been given. This experience indicated that an analysis of the blood for organic phosphorus might be misleading, and that when viosterol was being given, the presence of rickets would have to be determined by clinical signs and the roentgenogram. It also showed not merely that rickets was a systemic disease, but that local factors played a determining rôle in calcification at the epiphyses.

De Sanctis and Craig⁶⁶ compared the efficiency of viosterol and cod liver oil as prophylactic antirachitic agents, using comparatively large groups of infants as subjects. The children were all similar in age and rate of growth, and the duration of the experimental period in each instance was the same. Of 123 children to whom viosterol was administered, 29 per cent were not protected against rickets, while of 100 given cod liver oil, only 3 per cent showed rickets although the previous group received twice the number of units of vitamin D as the latter. The authors were inclined to believe that these results indicated that other circumstances in addition to lack of vitamin D were responsible for the development of rickets.

According to Brown and Shohl,⁶⁷ vitamin D controlled calcification of the skeleton by dissolution and deposition of bone salts. The mineral content of bone was the result of these two actions. It was equally important that calcium and phosphorus should be present in the diet in

65 Hess, A. F., Lewis, J. M., and Rivkin, H. Newer Aspects of the Therapeutics of Viosterol (Irradiated Ergosterol), *J. A. M. A.* **94** 1885 (June 14) 1930.

66 De Sanctis, A. G., and Craig, J. D. Comparative Value of Viosterol and Cod Liver Oil as Prophylactic Antirachitic Agents. A Clinical Study, *J. A. M. A.* **94** 1285 (April 26) 1930.

67 Brown, H. B., and Shohl, A. T. *J. Biol. Chem.* **86** 245 (March) 1930.

sufficient amounts and in appropriate relationship to each other in order that growth or calcification of the bone could occur. No amount of vitamin could correct an absolute lack of bone-building salts. As expressed by Brown and Shohl, the amount of calcium and phosphorus in a diet determines the retention of these elements. Vitamin D controls the intermediary metabolism.

Jones and his associates⁶⁸ studied the effect of viosterol before and after thyroparathyroidectomy in dogs kept on a basal ration containing 0.25 per cent calcium of viosterol. Given before operation, viosterol tended to delay tetany and prolong the life of the dogs. The dogs could be kept alive indefinitely and apparently in good health after parathyroidectomy by repeated dosage with viosterol. The only untoward effect of the hypercalcemia was a loss of appetite. No constant effect on the concentration of the inorganic phosphorus was noted. The authors concluded that the action of viosterol could not be due to a stimulation of the parathyroid glands.

Experimental Epiphyseal Displacements and Rickets Induced by Strontium.—Benassi,⁶⁹ experimenting with rabbits, produced traumatic displacement of the upper epiphysis of the tibia, and fed strontium to produce epiphyseal changes which had been previously reported as similar to those of rickets. He concluded that strontium poisoning did produce in small rabbits osseous alterations with histologic changes and a roentgenologic picture typical of human rickets. The experimental traumatic epiphyseal detachment occurred with great regularity in the cartilaginous area, generally in the stratified zone or less frequently in the vascular juxta-epiphyseal stratum. The detached fragment, left to itself, restored itself spontaneously to its normal position, and remained there without need of retaining apparatus. Roentgenologically, the only evidence of detachment was a slightly wider space at the epiphysis than on the normal side. The healing process was similar to that of the repair of a fracture. The crevice filled with blood and exudate, which tended to become organized. Subsequently the various strata were reconstituted by the proliferation of the cartilage itself, and when healing was completed only a little irregularity remained to show that there had been an injury. In none of the animals did the epiphysis close or become completely ossified, and there were no examples of failure of epiphyseal growth. The rachitic changes induced by the strontium were more evident on the traumatized side than on the normal side. The strontium influenced the process of cure of the detachment. The consolidation occurred more irregularly and more rapidly with an exuberant and disordered callus.

68 Jones, J. H., Rapoport, M., and Hodes, H. L. *J. Biol. Chem.* **86**: 267, 1930.

69 Benassi, E. *Chir. d. org. di movimento* **14**: 397 (Jan.) 1930.

Penetration of Ultraviolet Light Through the Human Skin—In a carefully controlled study, Bachem and Reed⁷⁰ determined the depth of penetration of ultraviolet light through human skin. They found that most of the visible light was absorbed in the corium, some of the longer visible rays penetrating into the subcutaneous layers. Most of the near ultraviolet was absorbed in the malpighian layer. The waves around 275 millimicrons were practically all absorbed by the corium and granulosum. Light waves of this length had been credited with the greatest antirachitic activity. Many light waves between 260 and 300 millimicrons penetrated to the stratum germinativum. This was the portion of the light spectrum which produced the most erythema. Practically no light waves shorter than 230 millimicrons were able to penetrate the corium.

The Resorption of Bone—In an exhaustive pathologic study on the resorption of bone, Jaffe⁷¹ found two types of resorption, one in which resorption was accomplished by blood vessels and granulation tissue with little or no help from the osteoblasts, and a second in which osteoblasts played the chief rôle. Resorption by blood vessels was found to be the more important type. The caliber of the blood vessels increased, and new vessels, so-called Volkmann's canals, were seen. Resorption seemed to be dependent on a previous decalcification, but just how this occurred in vascular resorption was not understood. The decalcified organic matrix was removed by tissue enzymes or by phagocytes in the invading granulation tissue. Osteoclastic resorption was dependent on the reaction of the tissues by the calling out of osteoclasts. The author was unable to tell why osteoclastic resorption appeared to play the dominant rôle in certain cases. Howship's lacunae were formed in the endosteal or periosteal surfaces of the bone by erosion. It was still unsettled whether the erosion took place by the osteolytic action of osteoblasts or whether the bone was simply phagocytosed. A preceding decalcification of the bone seemed to be necessary for the formation of Howship's lacunae. The osteoclasts had been observed developing from mesenchymal connective tissue and from the fusion of resting wandering cells. Eventually, their function completed, they either disintegrated or entered blood vessels and were removed.

Fate of Free Cartilage Transplant in Joint—Harbin and Moritz⁷² performed a series of experiments on dogs to determine whether cartilage would survive in joint cavities unattached to the synovial membrane. A small piece of cartilage was removed from the femoral condyle

70 Bachem, A. and Reed, C. I. Arch. Physical Therapy **11** 49 (Feb.) 1930

71 Jaffe, H. L. Resorption of Bone. Consideration of the Underlying Processes Particularly in Pathologic Conditions. Arch. Surg. **20** 355 (March) 1930

72 Harbin, M. and Moritz, A. R. Autogenous Free Cartilage Transplanted into the Joints. An Experimental Study. Arch. Surg. **20** 885 (June) 1930

enclosed in a collodion sac and placed in the opposite knee joint. A second piece of cartilage of equal size was placed in the cavity of the knee joint, without any protective covering. The authors found that a piece of articular cartilage would survive, nourished only by the diffusible elements of the joint fluid for as long as thirty-two days, but no proliferation of cells occurred. When the collodion sac became broken permitting direct contact with the synovial fluid, superficial, fibrous connective tissue proliferation occurred. This offered an explanation for the spontaneous production and growth of the joints of mice. A system of interlacunar canaliculi providing for the circulation of fluids in the cartilage matrix was observed in the pieces of cartilage.

Fascial Transplants Autogenous and Prepared—Haas⁷³ studied the union of fascial grafts with muscle. In a series of six dogs a strip of fascia lata, from which the fat had been scraped with a knife, was sutured across a gap in the semimembranous or semitendinosus muscle and tendon. The author found definite cellular union between muscle and fascia, first apparent in about three weeks. The connective tissue cells of the fascia, perimysium and endomysium contributed most to the union of fascia and muscle. In two cases in which a Mayer operation on the shoulder had to be revised, a similar union of fascia and muscle was found.

Dainelli⁷⁴ reported a series of experimental arthroplasties on rabbits using strips of fascia lata previously fixed in formaldehyde and sterilized. Dainelli's conclusions were: The interposed sheath acted only mechanically to prevent contact of the ends of the bones. The fascia which had been subjected to fixation was completely absorbed within thirty or forty days, but not before the articular head had been covered with fibrous tissue so that ankylosis was securely prevented. Restoration of the articular surfaces occurred through cartilaginous metaplasia so as to permit within the limits of the experiments an almost normal recovery of the articular movement. Use of prepared fascia in arthroplasties therefore seemed advisable, since in comparison with other material, such as free fascial transplants, it had the advantages of instant availability in the operative room without the necessity of lengthening the operation by having to make a second incision to procure it.

73 Haas, S. L. *California & West Med* **32** 387, 1930.

74 Dainelli, M. *Chir. d. org. di movimento* **14** 555 (March) 1930.

RECURRENCE OF VARICOSE VEINS FOLLOWING INJECTION

A STUDY OF THE PATHOLOGIC NATURE OF THE RECURRENCE AND
A CRITICAL SURVEY OF THE INJECTION METHOD

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A study of the end-results of our treatment of varicose veins by the injection method during the past three years has revealed a startling percentage of recurrences. In a small series of sixty-six cases, recurrence has been observed a year or more after thrombosis in fifty-two patients. These results are in such contrast to the enthusiastic reports of the treatment of varicose veins by injection that a critical review of the therapeutic thrombosis of varicose veins seems justified. The wave of enthusiasm that several years ago greeted the treatment of varicose veins by the injection of sclerosing agents gave the method an impetus that has not been justified by the ultimate results, and it is becoming increasingly evident that a more careful elimination of unsuitable cases and a return to surgical procedures combined with injection of sclerosing agents is necessary to obtain satisfactory and more permanent results.

METHOD

The treatment of these patients was begun in November 1927, at the suggestion of Dr. Emile Holman, in an effort to compare this method with the results known to be obtained by operation. A careful history was obtained in each case and a general physical examination made with records of blood pressure, urinalysis, leukocyte counts and Wassermann tests. In addition, before beginning treatment, a careful history of factors related to varicose veins was obtained on a special blank form and the position of the varices, ulcer and areas of eczema recorded on a special graphic chart. These charts were a modification of those suggested by Nicholson.¹ The patients were examined also

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¹ Nicholson B B. Varicose Veins. Etiology and Treatment. A Clinical and Histologic Study. Arch Surg 15:351 (Sept.) 1927

by the usual Tiendelenburg procedure to test the competency of the saphenous and perforating valves, and by the tourniquet constriction walking test, or by the use of pressure bandages over a period of from two to four days, to test the patency of the deep veins

A 20 per cent solution of sodium chloride has been used as the sclerosing agent in the treatment of these sixty-six patients. It was found convenient to enter the veins with the patient standing, while the injection was made in the supine or sitting position with the legs elevated. Various procedures for promoting thrombosis were utilized, such as "stopping" the vein with the finger proximal to the point of injection, the application of the tourniquet, the use of hot 20 per cent saline solution at from 105 to 110 F, and massage about the site of injection following withdrawal of the needle. Pressure bandages were used for at least two weeks after thrombosis in an endeavor to obtain collapse of the veins with agglutination and organization of the wall of the collapsed vein. In the beginning, patients were admitted to the hospital wards and were given injections at intervals of from one to two days. Forty-three patients were treated in the hospital. After becoming familiar with the technical difficulties and the dangers of the new method and convinced that satisfactory thrombosis could be easily produced, ambulatory treatment of the patients was begun. The patients were as thoroughly examined as in the hospital admissions, and one afternoon a week was devoted to the ambulatory treatment. Patients were treated once a week. From one to three injections were given at a sitting and from 10 to 12 cc of the sodium chloride solution at a single injection.

With the method described, thrombosis of varicose veins was easily obtained. A few cases were at first refractile to the treatment, and thrombosis was secured by injection of 30 per cent dextrose, quinine and urethane, or by repeated injections of salt. Complete thrombosis was obtained in forty-eight cases. One patient had varicose veins remaining after the excision of a femoral arteriovenous fistula, and in this instance complete thrombosis was not thought desirable. In several of the early patients incomplete thrombosis was obtained because of our unfamiliarity with the method. The remainder of the eighteen patients in whom thrombosis was incomplete represent patients who stopped treatment and those who had such large varicosities with ulceration, hard brawny edema of the leg and completely incompetent valves that although the greater number of veins were thrombosed, the older thrombi recanalized or were absorbed before injections were complete. These last patients are still being treated.

Injections were considered complete when all visible and palpable veins with the exception of small telangiectases were thrombosed. Thrombosis of the internal saphenous in the thigh was attempted even

if the vein was not dilated or visible. Many of the patients showed thrombosis of the saphenous veins up to the saphenous bulb at the entrance into the femoral vein. Complete thrombosis was obtained in forty-eight patients 72 per cent of the cases. A few of the eighteen patients classed as having incomplete thrombosis had one or two isolated veins or perforating veins still patent although the remaining veins were well thrombosed.



Fig 1—*A* shows the patient before injection with marked bilateral varicose veins incompetent saphenous and perforating veins and dilated saphenous bulbs in both groins. In *B* the arrow points to the dilated saphenous bulb. *C* shows the result from reoperation after complete recurrence.

One outstanding example was a patient in whom the entire saphenous system was dilated with large tortuous veins below the knee and very prominent saphenous bulbs (fig 1). Twice the patient had been told by physicians that he had bilateral femoral hernias and was advised to submit to operation. A third physician had prescribed a double truss which the patient wore over the saphenous bulbs for some months with discomfort. In this man complete thrombosis of all veins

of the saphenous system of both legs was obtained, yet these same varicosities recurred within eight months after thrombosis. Injection was repeated with equally satisfactory immediate results, and within four months the saphenous vein on the right had recanalized to below the knee with beginning recurrence in the varicosities of the left leg. It is only because of the completeness of the thrombosis obtained in these cases that we have the temerity to report such a high percentage of recurrences, and to feel that the fault is not in the method or in the solution used, but in the natural reparative processes of the body.

A comparison between the patients treated by injection every one or two days and the patients receiving weekly treatments shows the average number of injections to be four per patient for the patients in the ward, while the average number of injections for the ambulatory outpatient series was eight. Satisfactory thrombosis was secured in an average of four and one-half days in the hospital series, while patients coming to the outpatient department were under treatment for an average of 66 weeks. Thus it is evident that private patients may have their veins thrombosed easily within a week by daily injection, and it suggests that an outpatient varicose vein clinic would be managed to a better advantage as a daily clinic.

RECURRENCES

Patients in whom complete thrombosis was obtained were asked to report back in three months, six months and a year. They were prompt about keeping the appointment after three months, but the majority did not appear after six months or a year. It was noticed that those who did return after six months showed beginning or complete recurrence. In December, 1929, we made a definite, organized attempt to see and examine all patients whose veins had been thrombosed by injection a year or more before. In the follow-up studies, seventeen of the sixty-six patients could not be located. It was known from the records that four of the seventeen had early recurrences. One patient was seen nine months after completion of treatment with firm thrombosis and without recurrence, and this patient is classed with those followed for a year or more. In the remaining forty-eight patients recurrence was demonstrated in every case. The actual recurrence rate, then, is 79 per cent of all patients, or 98 per cent of those followed for a year or more. The average time of observance of recurrence was ten and one-half months. The shortest period before observation of recurrence is three months and the longest twenty-four months. Collapse and adherence of the walls of the vein occurred in only three cases, and in these the collapse affected only segments of the vein.

It is of interest that in patients who had competent valves of the perforating set but incompetent valves of the saphenous vein recurrences

developed with as great a regularity and within the same space of time as in those who had incompetent valves in both perforating and saphenous veins

The one person who had a satisfactory and complete thrombosis happened to have a single dilated straight saphenous vein in the right calf with competent saphenous and perforating valves. This man was seen nine months after thrombosis but cannot be located now.

COMPLICATIONS

Mention should be made of the complications encountered in this series. Perivenitis apparently more alarming and painful than dangerous occurred in eighteen cases. Rest in bed with compresses and elevation of the legs brought relief, but the process often lasted from three to four weeks before completely subsiding. Sloughs were produced by perivenous injection or leakage along the needle track in eleven cases. All but one of these were small. Separation of the slough took place in from three to four weeks and for complete healing from eight to ten weeks were necessary. Definite nonfatal pulmonary embolism with frothy bloody expectoration, pleural pain, physical and roentgenographic signs of consolidation of one lobe of the lung occurred in one person. A second patient whose case report follows received four injections and a slough resulted at one point from extravasation into the tissues.

At the time of this patient's admission to the hospital physical examination revealed enlarged reddened tonsils and an injected pharynx. The white blood count was 17,750. She was discharged from the hospital and requested to return in one month for tonsillectomy. She lived at a distance of ninety miles, and instructions were given as to the care of the slough. She returned in one month with the story that she had had severe sore throat for one week with slight substernal pain, an unproductive cough and tenderness and swelling of the right wrist. The day of readmission to the hospital she suddenly became short of breath with palpitation and very rapid heart beat. Physical examination showed that she was acutely ill and dyspneic and that there was marked heaving of the precordium that could be seen through the bed clothes. Her throat was intensely injected. There was dullness at the upper lobe of the right lung with suppression of the breath sounds. The heart was enlarged to the left. The extremities were normal, except for the irregular ulcer on the left shin which had a sloughing base. The urine was normal when examined. The white blood count was 28,000 with 95 per cent polymorphonuclear leukocytes. The temperature was 38 C (100.4 F), the pulse rate 160 and the respirations 50 per minute. The patient's condition remained the same to the fourth day after admission when she began to cough up bloody frothy material. Over the upper part of the right side of the chest there appeared bronchovesicular breathing and an increased transmission of voice sounds to auscultation. The blood culture showed no growth. A culture from the throat showed streptococci of the green pigment-producing type with non-hemolytic streptococci. Culture of the ulcer on the leg showed *Bacillus coli*. The patient died of cardiac failure on the fifth day after admission. Autopsy could

not be obtained. The final hospital diagnosis was sepsis, acute follicular tonsillitis and pharyngitis, ulcer of the leg, acute endocarditis and questionable pulmonary infarct.

SYMPTOMATIC RELIEF

It is interesting to contrast the symptoms before and after injection. Such a comparison gives a more optimistic picture of the value of therapeutic thrombosis of varicose veins. Sixty-four of sixty-six patients complained of symptoms other than the presence of unsightly veins. Thirty-five complained of burning pains in the course of the veins. Fifty-eight suffered from pain and fatigue in the legs when working or while standing for hours. Spontaneous hemorrhages had occurred in five persons. Ulceration had occurred in twenty-six cases, and in three people there were ulcers on both legs. Swelling of the ankles at the end of the day was experienced by forty-eight patients, and eczema of the legs was an added burden in sixteen.

Symptomatic relief lasting a year or more occurred in forty-nine patients of whom we have definite records. Eight of these patients still had pain, ten experienced fatigue of the calf muscles when standing for hours, and four patients had itching of the legs. In six patients, ulcers had recurred. One person still suffered occasional cramps in the leg. In thirty-seven patients, the veins were visible as definite large varicosities, and in fifty-two, it was possible to determine by palpation that the lumen of the veins was patent and to demonstrate a transmitted impulse in the recurrent veins by tapping with the finger on the saphenous vein in the thigh.

Complete relief from symptoms was obtained in twenty-eight, and partial or complete relief in forty-nine of fifty-two patients. Many of the patients were greatly surprised when asked to return for reinjection or operative excision of the recurrent veins. We do not feel that this relative freedom from symptoms is a guarantee against progressive enlargement of the recurrent veins or the usual varicose complications of ulcer, eczema or edema.

MICROSCOPIC STUDY OF INJECTED VEINS

Efforts to obtain permission from our patients to excise segments of thrombosed veins under local anesthesia did not meet with much success, and the material was supplemented with excised segments of thrombosed veins secured by Dr. E. J. Mahon from the U. S. Marine Hospital, San Francisco. Microscopic paraffin sections were utilized in the study to determine the process of thrombosis and recurrence.

Thrombosis of the veins, except as noted, was obtained by injection of 20 per cent sodium chloride, and all of the veins selected for microscopic examination were found to be firm and hard within twenty-four hours after injection.



Fig 2—Low power photomicrograph taken forty-eight hours after injection. The lumen of the vessel is filled with a red thrombus, leukocytic infiltration is progressing. This and the following photomicrographs were supplied by Dr Frank E. Blaisdell.

Twenty-four hours after injection, the vein was palpated as a firm, hard, slightly tender cord, and gave no impulse on percussion. Microscopic sections showed the lumen of the vein to be filled with a red thrombus composed of closely packed red blood cells with areas of hyaline bluish lines of Zahn. The intima was partially destroyed, and the regularly spaced endothelial cells were visible only in small portions of the vein. Fine tiny threads of fibrin reached out from the wall of



Fig 3—High power photomicrograph taken seventy-two hours after injection. The fibrin network is rendered distinct by agglutination of pigment granules along the fibrin threads. Splitting of the vessel wall is shown, with a beginning ingrowth of endothelial cells.

the vein into the thrombus. The vasa vasorum were engorged and there was edema of the adventitia and perivascular tissues.

Forty-eight hours after injection, the sections showed essentially the same picture as the twenty-four hour specimen, the red cells were collected into large, irregular, homogeneous groups, the cell outlines being indistinct, and innumerable fine pigment granules were seen

throughout the thrombus which tended to collect about white cells, the fibrin threads and the lines of Zahn (fig 2)

Seventy-two hours after injection, the fibrin network of the thrombus was made more distinct by the collection along the fibrin strands of the pigment granules (fig 3) Phagocytic cells were invading the thrombus and an occasional invading endothelial cell could be made out near the periphery of the thrombus The vasa vasorum showed swell-



Fig 4—Low power photomicrograph taken six days after thrombosis Cleavage spaces at the periphery are lined with endothelium and contain fresh blood The arrows point to cleavage space and new vessels

ing and proliferation of their endothelial cells, the lining of the vessels almost resembling cuboidal epithelium

Six days after injection, the thrombus showed the red cells to be in homogeneous masses with indistinct cell outlines Leukocytic infiltration of the thrombus was well advanced, and the pigment granules were found in larger masses within the phagocytic cells Cleavage spaces had appeared between the thrombus and the wall of the vessel and were filled with fresh red blood cells (fig 4)

Nine days after thrombosis, the vasa vasorum were markedly engorged and distended. The red thrombus filling the lumen had retracted from the wall of the vessel, leaving two large, crescentic lacunar-like spaces between the thrombus and the vessel wall which were lined with endothelium and filled with fresh blood. The two broad points of attachment of the thrombus to the wall of the vessel showed

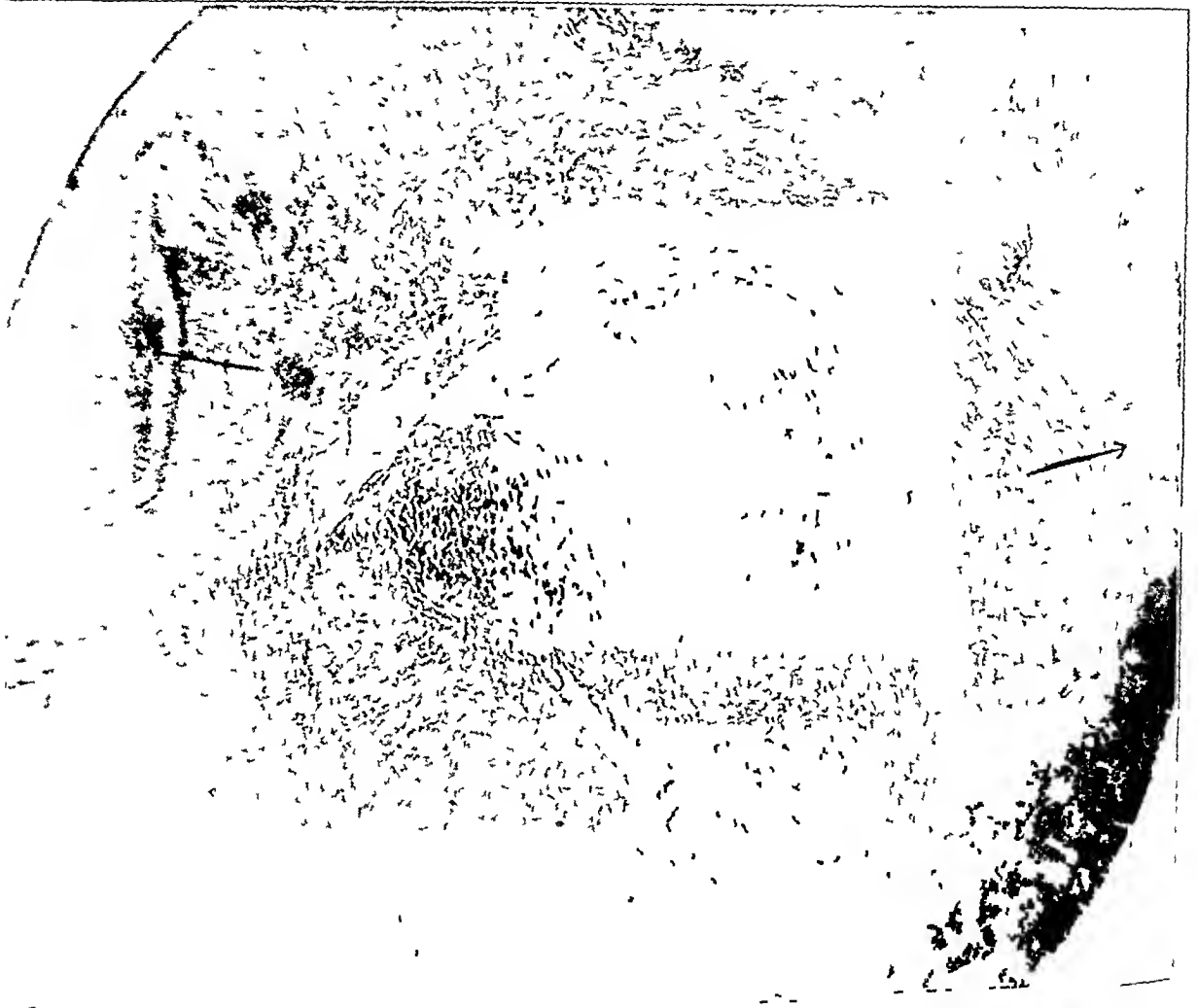


Fig 5—Low power photomicrograph taken three weeks after thrombosis. There is a peripheral zone of organization with new blood vessels, fibroblasts and a central zone of unorganized thrombus with apparent softening. Such softening may lead to opening up of considerable lumen by absorption of the softened thrombus (Welch). The arrows point to new lacunar vascular sinuses lined with endothelium and containing fresh blood.

an advancing invasion of numerous tiny capillaries and endothelial cells along the fibrin strands into the thrombus.

Thirteen days after thrombosis the thrombus was still composed mainly of hyaline homogeneous masses of red blood cells with faint

outlines, and leukocytes caught in the fibrin network. The thrombus had separated from the vessel wall along two thirds of its circumference and remained attached by a broad pedicle. The lacunar space formed by this separation was filled with fresh blood and lined with endothelium, and new capillary vessels were growing from the endothelial lining of the space and from the broad pedicle of the thrombus out into the fibrin network. The proliferation of fibroblasts was advancing with



Fig 6—High power photomicrograph taken three weeks after thrombosis. Organization is proceeding from the old intima. Large spaces are seen lined with endothelium and containing fresh blood.

the new capillary vessels. Many of the new blood vessels were relatively large and all contained fresh blood cells.

Three weeks after thrombosis, the center of the thrombus was still composed of masses of hyaline, faintly staining red blood cells. There were fairly large lacunar spaces at the periphery of the thrombus, lined with endothelium and filled with fresh blood. The new vessels growing from the intimal surface of the vessel penetrated for some distance into the thrombus and were accompanied by fibroblasts (figs 5 and 6).

Five weeks after thrombosis, the thrombus was invaded from almost all portions of the intimal surface of the lumen by small capillary vessels. Fibroblastic proliferation had taken place and for over half the circumference of the wall of the vessel definite organization had advanced a short distance into the thrombus. A bridge of organized fibroblastic



Fig 7—Low power photomicrograph taken five weeks after thrombosis. Partial organization is seen advancing from the periphery and from the organized vascular fibrous bridge. There is a small central "Y" shaped lumen lined with endothelium. One large lacunar endothelial lined space is seen. To the left the unorganized thrombus shows signs of apparent softening.

tissue with numerous small blood vessels bisected the lumen of the vessel (figs 7 and 8).

Eight weeks after thrombosis, complete organization had taken place. The site of the previous intimal coat was marked by newly formed tissue



Fig 8—High power photomicrograph taken five weeks after thrombosis. The vascular fibrous bridge, the lacunar endothelial lined space, and organization advancing from the old intima into the thrombus are shown.

composed of small capillary vessels, large blood vessels that formed distinct vascular sinuses, and by a marked invasion and proliferation of fibroblasts. Although organization was almost complete, there was an



Fig 9—Low power photomicrograph taken eight weeks after thrombosis. The lumen is reestablished and the remains of the thrombus are seen as an organized mural thrombus with one small pedunculated mural thrombus.

irregular lumen about one-third the size of the original lumen, it was lined with endothelium and its walls were formed by the fibrous granulation tissue of the organized thrombus (fig 9). A pedunculated mural thrombus could be seen.

Eight weeks after thrombosis, the fatty tissue about the adventitia had areas of dense perivascular round cell infiltration. The muscularis of the media had numerous small blood vessels penetrating the circular muscle in an oblique direction. The old intimal margin marked the beginning of a vascular granulation tissue. Numerous blood spaces lined with endothelium and containing fresh blood had appeared. One

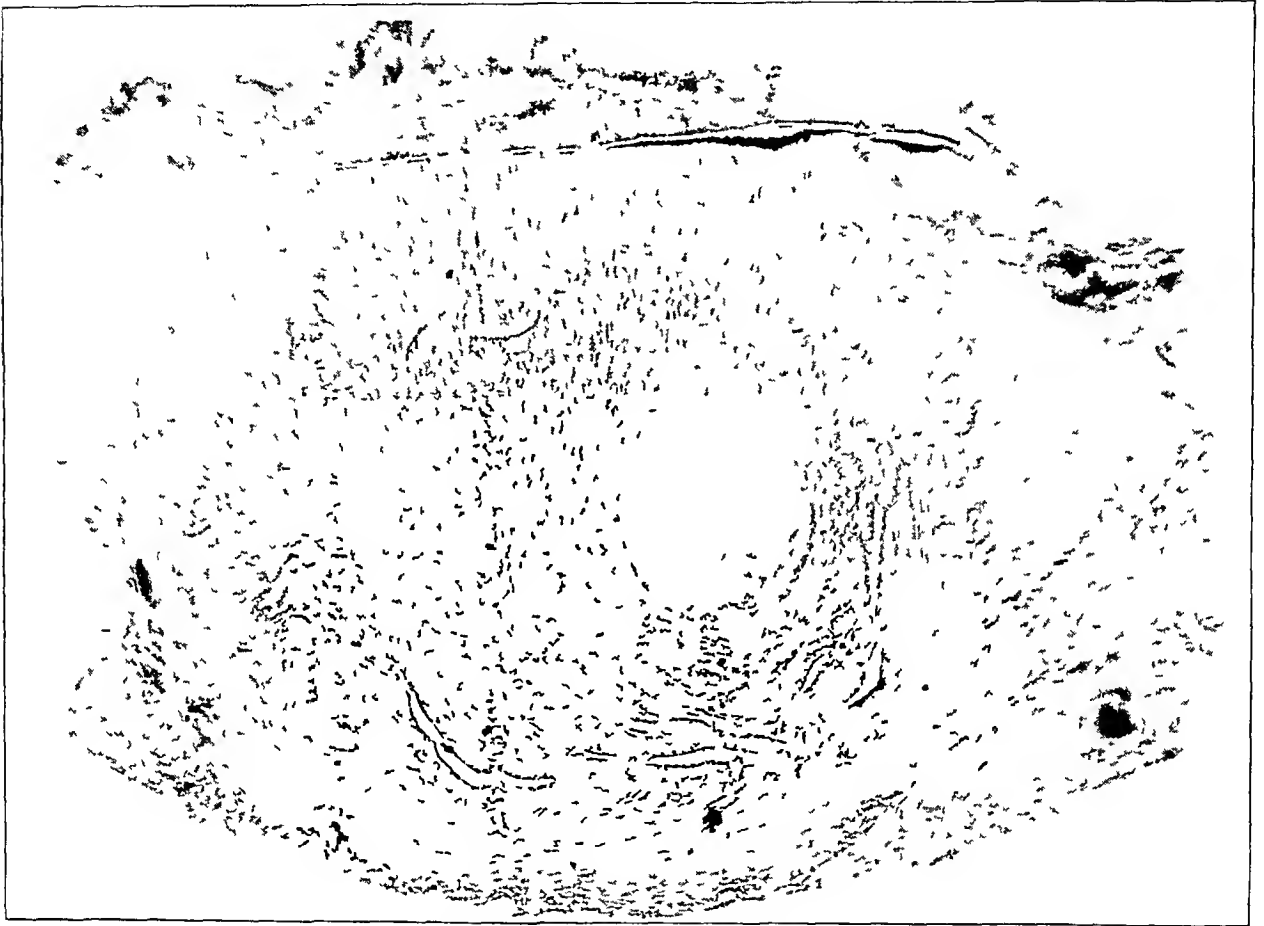


Fig 10—Low power photomicrograph taken eight weeks after thrombosis. Almost complete organization of thrombus by highly vascular tissue is seen. Sinuses and lacunar spaces are seen. A large eccentric lumen is lined with endothelium, contains fresh blood, and apparently was formed by absorption of a softened portion of the thrombus.

large circular blood space, a fifth of the size of the old lumen, was patent (fig 10).

Three and one-half months following thrombosis with sodium chloride 30 per cent and dextrose 50 per cent, there was a proliferative endovenitis concentrically narrowing the vessel lumen by about one-fifth. The remaining four-fifths of the lumen contained fresh red

blood cells. There was a definite laying down of fibrous tissue along the delicate new blood vessels, and fresh red blood cells were found between the meshes of the fibrovascular tissue. There was a marked periventitis with pronounced perivascular round cell infiltration in the adventitia and surrounding fat (fig 11).

Four and one-half months following thrombosis with 30 per cent sodium chloride and 50 per cent dextrose, the adventitia showed a moderate periventitis. The lumen of the vessel showed fibrosing endoventitis with scanty small blood vessels which narrowed the lumen by about one-fourth. There was one pedunculated mural thrombus fixed by a broad base which showed partial organization. The remaining three-fourths of the vessel lumen was patent and contained fresh blood (fig 12).

Nine months after injection with sodium salicylate, complete organization and fibrosis of the thrombus had occurred. The strands of fibrous tissue and nuclei were arranged in a radial direction from the center of the lumen, and only small blood vessel sinuses were seen, with a tiny central lumen. This patient had had three operations for varicose veins, and the vessel thrombosed by injection was a single, isolated vessel running between the scars of previous operations.

Ten months after thrombosis with 20 per cent sodium chloride, the wall of the vessel still showed the site of the old intima marked by the beginning of a dense fibrous tissue with the fibrin bundles and nuclei pointing toward the lumen. At the junction of the old intima and the fibrous tissue, there were numerous vessels and small blood sinuses. A good sized lumen, about one third of the old lumen in caliber, was lined with endothelium (fig 13).

REPORTED RECURRENCES

In the extensive literature on the treatment of varicose veins by injection, most authors have directed their attention to the method of accomplishing the thrombosis, the solution advocated and the question of embolism. Scant notice has been given to end-results, and few studies are available. P. Linser² and Zinn³ in reporting the results obtained at Linser's clinic from 1916 to 1925, in over 1,300 cases following the injection of mercuric chloride, do not present a follow-up

² Linser, P. Ueber die konservative Behandlung der Varicen. *Med. Klin.* **12** 897, 1916; Die Behandlung der Krampfaderen mit Sublimatenspritzungen und ihre Erfolge, *ibid.* **17** 1445, 1921; Die Behandlung der Varizen mit künstlicher Thrombosierung, *Dermat. Ztschr.* **45** 22, 1925.

³ Zinn, Camillo. Die Behandlung der Krampfaderen mit intravenösen Sublimatinjektionen, *Dermat. Ztschr.* **23** 650, 1916; *München med. Wchnschr.* **66** 382, 1919.

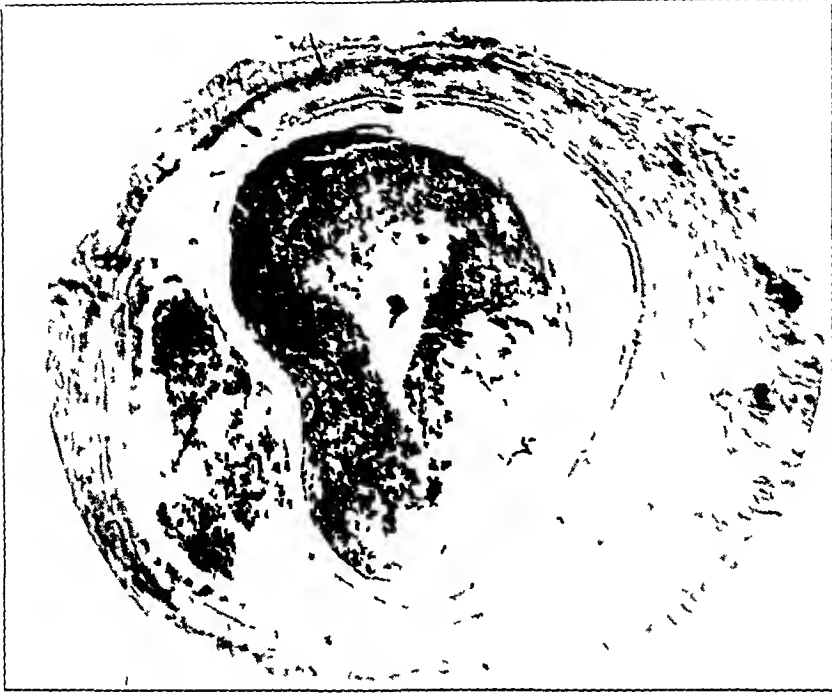


Fig 11—Low power photomicrograph taken three and one-half months after thrombosis. The vessel lumen is narrowed by an organized vascular mural thrombus. The lumen is patent and contains fresh blood.



Fig 12—Low power photomicrograph. There is an organized vascular mural thrombus narrowing the vessel lumen.

study of these cases. They mentioned that they have many early cases in which the patients are free from complaints for several years and are able to work, and that from three to four years after injection the patients may show recurrence in collaterals in the veins that have not been treated, but that the treated veins have disappeared or are palpable

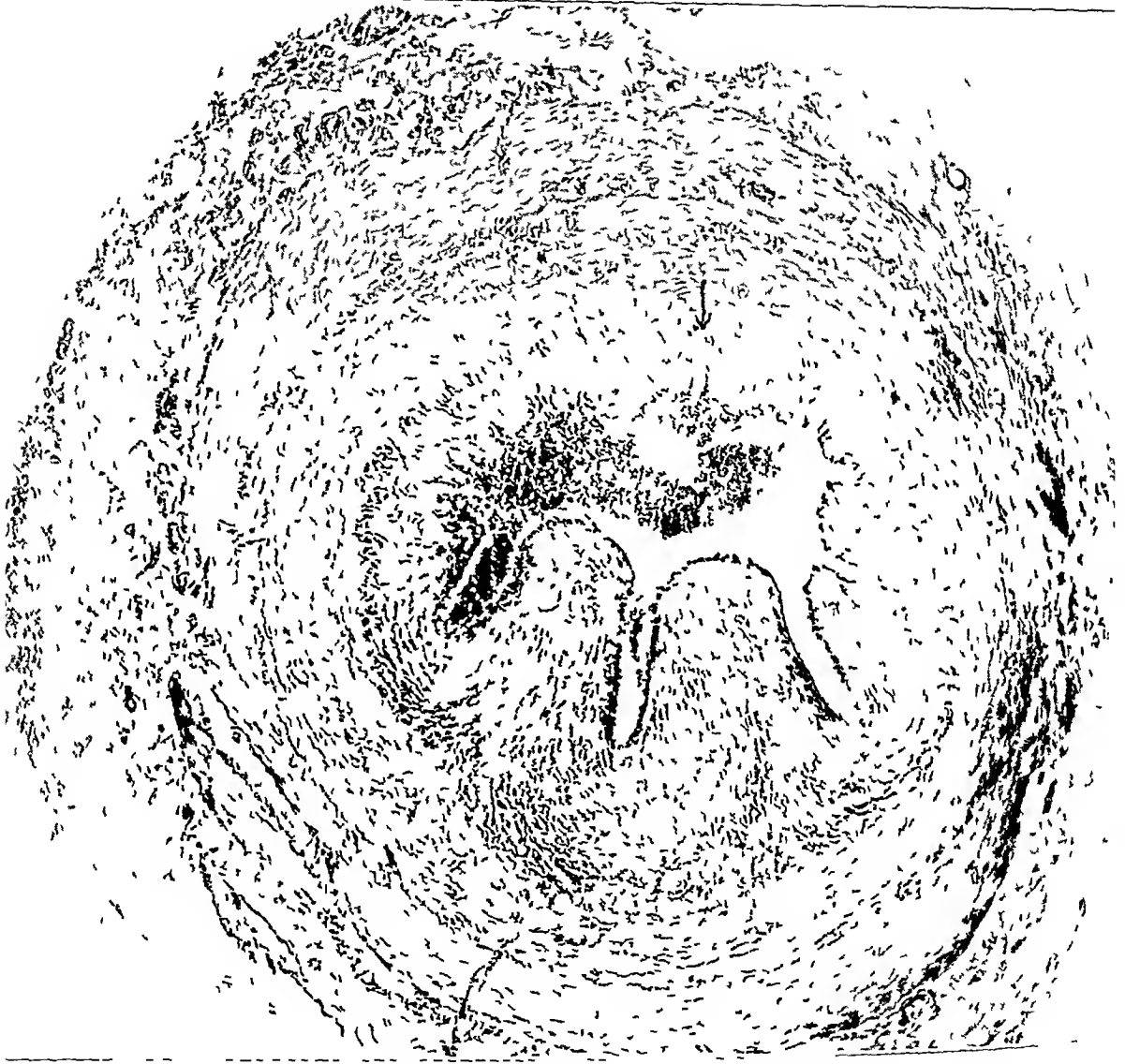


Fig 13—Low power photomicrograph taken ten months after thrombosis. The site of the old intima marks the origin of an irregularly festooned mural thrombus. The organized thrombus still contains numerous blood vessels.

as thin cords. K. Linser,⁴ after two years' experience with sodium chloride, did not mention recurrences and presented no survey of the

⁴ Linser, K. Zur Behandlung der Varizen mit Intravenösen Injektionen. München med. Wchnschr. 71 515, 1924, Die Behandlung der Krampfaderen mit intravariösen Kochsalzinjektionen, Dermat. Wchnschr. 81 1345, 1925.

final results Hemple⁵ expressed the belief that not sufficient time has elapsed to judge of the permanency of the results and stated that collaterals developed in 12 per cent of his cases Fischer,⁶ who used mercuric chloride, had a number of patients in whom for from three to five years after treatment one was able to feel thrombosed cords, and who were free from symptoms He gives no statistics as to permanency of results Using calorose, an invert sugar, Nobl⁷ of Vienna obtained excellent results in 90 per cent of 200 cases, but neglected to mention recurrences or the time of observation Sicard and Paraf,⁸ using 10 per cent sodium carbonate in 1917 and 1918, then changing to 20 to 40 per cent sodium salicylate, have treated several thousand patients No follow-up studies are made available Bazelis⁹ stated that after three years' experience with Sicard's method, no recurrences of veins or ulcers have been observed Delater¹⁰ laid the blame for recurrences on endocrine disorders, but he failed to state the number of recurrences or the endocrine factors involved In 500 cases observed over three fourths of a year, Meisen¹¹ observed no recurrences Forestier¹² based his results on more than 4,000 injections of sodium salicylate and found 15 per cent recurrences with new varices, not of the old obliterated veins Sodium chloride in 20 per cent solution gave Goodman¹³ from 10 to 15 per cent of recurrences The time of observation is not stated Woolsey and Millzner¹⁴ treated over 150 patients with 20 per cent sodium salicylate and with quinine and urethane with 6 per cent recur-

5 Hemple, Curt *Erfahrungen mit Sublimatinjektionen bei Varizen*, München med Wchnschr **71** 900, 1924

6 Fischer, Carl *Ueber Behandlungen der Krampfadern mit Sublimatinjektionen nach Linser und über Behandlung der Beimgeschwüre*, Wien klin Wchnschr **35** 11, 1922

7 Nobl, G *Zur künstlichen Thrombose der Varizen*, Wien klin Wchnschr **31** 295, 1918

8 Sicard, J A, and Paraf, J *Traitement des varices par l'injection intravariqueuse de carbonate de soude*, Bull et mem Soc med d hôp de Paris **44** 1369, 1920 Paraf, J, and Lermoyez, J *Traitement des varices par les injections phleboscлерosantes de salicylate de soude*, Gaz d hôp **95** 1573, 1922

9 Bazelis, M *Traitement des varices par les injections intravariqueuses*, Presse med **32** 358, 1924

10 Delater, G *Fibrose curative des varices*, Presse med **34** 693, 1926

11 Meisen, V *Injection Treatment of Varicose Veins and Their Sequelae on Basis of 500 Treated Cases*, Acta chir Scandinav **62** 17, 1927

12 Forestier, J *Varices of Lower Limbs Treatment by Obliterating Injections Based on Experience with More Than 4,000 Injections*, J A M A **90** 1932 (June 16) 1928

13 Goodman, C *Treatment of Varicosities of Lower Extremities*, Internat Clin **4** 284, 1928

14 Woolsey, J H, and Millzner, R J *Varicose Veins Their Chemical Obliteration*, California & West Med **30** 325, 1929

ence in less than fourteen months' time. In sixty-four cases in which 40 per cent sodium salicylate was used, twelve, or 18 per cent, showed recurrences in from three to five months as reported by Cooperman.¹⁵ Kilbourne¹⁶ concluded from the answers to his questionnaire that the recurrence rate is about 6 per cent and quoted Delater as having 5 per cent recurrences after five years. From a communication from Sicaid's clinic, he is informed of 1 per cent recurrences at the site of injection and 4 per cent new varices in 15,000 cases. McPheeters,¹⁷ who has published extensively on the subject, failed to mention the percentage of recurrences in his cases, and he is content to state in his monograph that patients are asked to return in from six months to a year, when new varices that have appeared may be readily treated. The most satisfactory study of the treatment of varicose veins by injection that has appeared is the work of De Takats.¹⁸ The last of his series of papers dealing with the subject gives the recurrence rate at 10.8 per cent in 389 cases. He has used the injection method for three years and combines injection with ligation and excision of the saphenous vein in mid-thigh when it is visibly dilated. De Takats stated that "recurrences were observed as early as six weeks, and as late as a year after injection. While it was impossible to reexamine all discharged patients, they were routinely asked to return every three months. It is probable that a comparatively larger number of patients with failures returned than those cured." Our experience does not bear out this last statement, for those patients who refused to return for observation because they considered themselves cured invariably had recurrences when we examined them at home.

COMMENT

The results of our follow-up examinations with the microscopic studies of the fate of therapeutic thrombosis convince us that treatment by injection unaided by ligation, excision or stripping of main venous channels, and perforating veins when incompetent, will not serve to obtain permanent cure in cases of varicose veins except in the few isolated cases of dilated single veins with competent saphenous and perforating valves. The microscopic studies of veins into which injection has been made have shown the natural history of the thrombus in regard

15 Cooperman, M. B. Injection Treatment of Varicose Veins, *M. J. & Rec* **129** 541, 1929.

16 Kilbourne, N. J. Treatment of Varicose Veins of the Legs. Considerations of Safety, *J. A. M. A.* **92** 1320 (April 20) 1929.

17 McPheeters, H. O. Varicose Veins, Philadelphia, F. A. Davis & Company, 1929.

18 De Takats, Geza, and Quint, Harold. The Injection Treatment of Varicose Veins, *Surg. Gynec. Obst.* **50** 545, 1930.

to its organization, that is, vascularization and recanalization, a fact so well known to pathologists and so tersely described in the classic article of Welch¹⁹ on thrombosis and embolism as follows

One of the most interesting adaptive pathological processes is the so-called organization of thrombi which is the substitution for the thrombus of vascularized connective tissue. The thrombus itself takes no active part in the process, but behaves as a foreign body. It is gradually disintegrated and absorbed, largely through the activity of phagocytes. The new tissue springs from the wall of the vessel or the heart, the tissue forming cells being derived from the endothelium and from other fixed cells in the wall. New vessels spring from the vasa vasorum. Lacunar spaces in the thrombus, or between the thrombus and the vascular wall, may become lined with endothelium, and also serve as channels for the circulating blood. These new vessels may establish communication with the lumen of the thrombosed vessels above or below the thrombus or on both sides. The new tissue which at first is rich in cells, becomes fibrous and contracts. The result may be a solid fibrous plug, or a cavernous structure with large blood spaces, or, by disappearance of the septa, a restoration of the lumen, with perhaps a few fibrosed threads or bands stretching across it, as in the normal cerebral venous sinuses.

The restoration of the lumen is the most frequent end-result in thrombosed veins that are subject to constant back pressure either through the proximal unthrombosed saphenous vein or the perforating veins by their communication with the deep set, when the valves of these veins are incompetent. This principle has caused De Takats to ligate the saphenous vein when it is palpable above the mid thigh, in addition to causing thrombosis by injection of the distal veins and to urge the complete removal of the main saphenous vein with eradication of the perforating branches, when both sets of valves are found incompetent. Several workers, especially Tavel²⁰ and Moszkowicz²¹ have ligated the saphenous vein at or near the fossa ovalis preliminary to injection, but with the purpose of preventing embolism rather than preventing recurrence, and credit should be given De Takats for formulating the particular plan of ligation and injection for more permanent relief from varicosities.

The most successful treatment of varicose veins by the methods available at the present time is by operation with removal of the saphenous segment from the fossa ovalis to the knee and eradication of the dilated veins below this point at a time when the perforating valves are

19 Welch, W. H. Thrombosis in Allbutt, Clifford, and Rolleston. *H. D. A System of Medicine*, ed. 2, New York, The Macmillan Company, 1909, vol. 6, p. 701.

20 Tavel, E. Die künstliche Thrombose der Varicen, *Berl. klin. Wchnschr.* **44** 181, 1907, Die Behandlung der Varicen durch die künstliche Thrombose *Deutsche Ztschr. f. Chir.* **116** 735, 1912.

21 Moszkowicz, L. Krampfaderbehandlung mit Zuckerinjektionen und Venerligatur, *Zentralbl. f. Chir.* **54** 1732, 1927.

still competent and ulceration, eczema and edema are yet undeveloped. For permanent results, such a procedure can have no substitute. Far too frequently incomplete measures, such as ligation, ligation with excision of small vein segments or multiple small excisions are carried out. The experience of the past has shown that these measures are often unsatisfactory. In spite of this the same procedures are carried out because of their relative ease, the patient's fear of extensive operations or their abhorrence of extensive scars and especially because of economic factors that prevent prolonged hospitalization.

SUGGESTED INDICATIONS FOR COMBINED INJECTION AND EXCISION

It is distressing that the majority of sufferers from varicose diseases are small wage earners or overworked housewives whose family resources prevent both hospitalization and means of care for their children while under treatment (an obstacle of some importance). The economic factors will many times determine in the future, as it has in the past, the available method of treatment. It is in this particular situation that the treatment of varicose veins by injection has proved of real value in obtaining relief from suffering and in maintaining ability for productive labor in persons pressed for available time for treatment and lacking financial resources to secure adequate early treatment for permanent relief. With the attitude of adopting the best available method to the particular case under the economic circumstances and using the method of complete operation when possible, we suggest the following indications:

- 1 When single or isolated dilated vein segments exist in the presence of completely competent valves, symptoms are rarely present. People presenting themselves for treatment of such varices do so mainly for cosmetic reasons. Treatment by injection may be employed entirely.

- 2 If the patient has moderate dilatation or tortuosity of the saphenous system, provided that the perforating valves are competent, interruption of the venous continuity at the saphenous opening, with injection into the veins below, may be carried out. The interruption of the venous flow may be by ligation with excision of a segment of the vein under local anesthesia, and the treatment may thus be entirely ambulatory. Such a procedure has been successfully carried out by De Takats with promise of lasting results. Tavel utilized this method in 1905, and noticed that in seven of twenty-five cases spontaneous thrombosis occurred distal to the ligation and apparently permanent cure resulted. Instead of making an injection into the veins distally after an interval of several days following the high excision, as is usually done, one may make the injection into the veins in the wound at the time of operation.

It should be emphasized that ligation and excision should be done at the fossa ovalis and all tributary vessels emptying into the saphenous vein at this point should be ligated and cut across as well. A double saphenous vein may be present in the thigh and midthigh ligation of a single vein may fail to give additional benefit. The group of superficial tributary veins emptying into the saphenous vein at the saphenous opening are known to have caused recurrence by opening up of collateral channels following operative excision when these tributary veins were not ligated.

Perhaps a more permanent way of interrupting the back pressure would consist in stripping the saphenous veins from the femoral opening to the knee and making the injection into the veins below this point. The procedure need not necessitate prolonged hospitalization. As De Takats pointed out, the endeavor is to prevent thrombosis and consequent embolism from the deep and proximal veins by early mobilization.

3 When varicose veins are accompanied by incompetency of both saphenous and perforating valves, the complete operation of stripping with excision should be carried out at the expense of temporary loss of time from employment. It is in this type of case that we feel recanalization will occur in spite of complete and repeated thrombosis and that complete interruption of the continuity of the vein is necessary. Injection into the isolated vein segments may follow such an operation.

4 Those people are poor subjects for operation who have long-standing varicosities with incompetency of both sets of valves and who have extensive chronic ulceration, eczema and a hard, brawny lymph edema approaching the elephantoid condition. The swollen, indurated tissues of the leg hide numerous venous channels and dilated perforating veins which are extremely difficult to eradicate, and in this type of patient the operative results are not brilliant. Such patients are considerably improved but not cured by injection. Injection should be supplemented by the use of sulphurated zinc paste stockings, rest in bed and elevation of skin grafting to hasten healing of ulcers. The edema subsides remarkably but not completely, even under ambulatory treatment, and with the subsidence of the edema the hidden veins become visible or palpable and can be treated by injection. With recurrence of varicose veins such a patient must receive another injection to hold the improvement gained.

5 Following apparently complete operative excision, varicosities sometimes make their appearance. When this occurs, the new veins are irregular in their distribution and in their connection with the deep set and offer a considerable obstacle to complete reexcision. This type of vein may be properly treated by injection, which will probably have to be repeated.

SUMMARY

In sixty-six patients treated for varicose veins by the injection of 20 per cent sodium chloride, we have been able to reexamine forty-nine a year or more after treatment

On reexamination, forty-eight of the forty-nine patients showed recurrence of their previously thrombosed veins. Four additional patients were known to have had early recurrence, but could not be located after a year.

The recurrence rate is 79 per cent of all patients treated, or 98 per cent of all those we have followed a year or more.

In contrast, forty-nine had partial or complete relief from symptoms attributed to the varicosities, twenty-eight of these patients being completely relieved from all symptoms.

Recurrence of veins thrombosed by injection was found to take place by recanalization, a natural pathologic response to thrombosis.

The interruption of the continuity of the vein by excision, especially in the presence of incompetent saphenous or perforating valves, is held to be vital in securing more permanent results.

Indications for combining excision with injection are suggested in an effort to afford permanent freedom from recurrence in persons who cannot afford, or reject, the complete excision of varicose veins.

THE FORMATION OF BONE UNDER THE INFLUENCE OF EPITHELIUM OF THE URINARY TRACT

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CHICAGO

The relative frequency of stones composed chiefly of calcium and phosphorus in the urinary tract as compared with their occurrence in other excretory systems such as the lower intestine, biliary and pancreatic systems and the salivary glands has made a study of the local metabolism of these elements by the urinary tract of some importance. I¹ have indicated elsewhere in a preliminary report the rather unexpected action of the urinary tract on certain connective tissues in the production of bone. These observations will be discussed in detail in this article, and further observations relative to osteogenesis will be presented.

The presence of bone elsewhere than in the skeleton has been of considerable interest to the students of osteogenesis. An extensive literature dealing with this subject exists, of which a few striking examples may be cited. Apparently the most frequent site of heteroplastic bone is the sclerotic artery,² next in order possibly comes calcified foci in the lung, and it is not infrequently seen in the dura mater.³ Not rarely it forms in the eye⁴ following severe destructive processes. It has been described in squamous carcinoma of the skin⁵ and in carcinoma of the breast, in the fallopian tube,⁶ lymph nodes, tonsils and

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1 Huggins, C B. Experimental Osteogenesis, *Proc Soc Exper Biol & Med* **27** 349, 1930

2 Poscharissky, J F. Ueber heteroplastische Knochenbildung. *Beitr z path Anat u z allg Path* **38** 135, 1905. Bunting, C H. The Formation of True Bone with Cellular (Red) Marrow in the Sclerotic Aorta, *J Exper Med* **8** 365, 1906. Buerger, L, and Oppenheimer, A. Bone Formation in Sclerotic Arteries, *J Exper Med* **10** 354, 1908.

3 Hulstead, A E, and Christopher, F. Calcification and Ossification of the Meninges, *Arch Surg* **6** 847 (May) 1923.

4 Poscharissky (footnote 2, first reference)

5 Nicholson. Ossification in Calcified Epithelioma, *J Path & Bact* **21** 387, 1917.

6 Asami G. Heteroplastic Bone Formation in the Fallopian Tube, *Am J M Sc* **160** 107, 1920.

live¹, in fibromyoma of the uterus and in laparotomy scars⁷. It has been stated⁸ that any area of calcification is likely to be replaced by bone no matter what tissue is involved.

New formation of bone occasionally occurs in the urinary tract in man or in connection with urologic procedures. Bone was first described in the pedicle attachment of a renal calculus to the pelvis by Phemister,⁹ in two cases. It has been described in the abdominal wall following operations on the bladder by Lewis¹⁰ and others¹¹. Chauvin and Rouslacroix¹² described five cases of ossification observed by them in three years, subsequent to cystotomy, in the abdominal wall.

BONE FORMATION IN THE URINARY TRACT UNDER EXPERIMENTAL CONDITIONS

Blessig¹³ first observed calcification in the kidney of rabbits killed from four to six days after ligation of the left renal artery. Salkovsky (1866) described calcium deposits in the kidney of rabbits poisoned with mercuric chloride, this has been confirmed by many observers¹⁴. Litten¹⁵ and others¹⁶ have described extensive calcification in the kidney, regularly following temporary arrest of the renal circulation. A demonstrable deposition of calcium¹⁷ may be present as early as thirty-six hours after a temporary anemia of one hour. The calcification occurs in and around necrotic tubules chiefly in two zones, one beneath the cortical surface and the other at the base of the pyramids. Wells¹⁷ stated that calcification produced by temporary anemia as well as by

7 Lewis, D. Myositis Ossificans, *J. A. M. A.* **86** 1281 (May 5) 1923.
Gruca, A. Myositis Ossificans Circumscripta, *Ann. Surg.* **82** 883, 1925.

8 Wells, H. G. *Chemical Pathology*, ed. 4, Philadelphia, W. B. Saunders Company, 1920, p. 439.

9 Phemister, D. B. Ossification in Kidney Stones Attached to the Renal Pelvis, *Ann. Surg.* **78** 239, 1923.

10 Lewis (footnote 7, first reference).

11 Kretschmer, H. L. Myositis Ossificans Following Suprapubic Prostatectomy, *J. Urol.* **20** 477, 1928.

12 Chauvin and Rouslacroix. *J. d'urolog.* **27** 465, 1929.

13 Blessig. Ueber die Veränderungen der Niere nach Unterbindung der Nieren Arterie, *Virchows Arch. f. path. Anat.* **16** 120, 1859.

14 Weichselbaum. *Centralbl. f. allg. Pathol. u. path. Anat.* **2** 9, 1891.

15 Litten, M. Ueber pathologische Verkalkungen und Kalkmetastasen. *Virchows Arch. f. path. Anat.* **83** 508, 1881.

16 von Werra. Ueber die Folgen des vorübergehenden und dauernden Verschlusses der Nierenarterie, *Virchows Arch. f. path. Anat.* **88** 197, 1882.
Eisen-drath, D. N., and Strauss, D. C. The Effects on the Kidney of Temporary Compression of Its Vessels, *J. A. M. A.* **55** 2286 (Dec. 31) 1910.

17 Wells, H. G., Holmes, H. F., and Henry, G. R. Studies in Calcification and Ossification, *J. M. Research* **20** 373, 1911.

certain poisons is probably analogous to calcification of organic material in urine rather than calcification of tissues with lime salts direct from the blood, since the epithelium and tube-cast deposits seem to contain calcium only as phosphate with no demonstrable carbonate. When the necrosis and calcification involve interstitial tissues, carbonate can be demonstrated.

An important experiment leading to the formation of bone and bone-marrow in the kidney through permanent ligation of the vascular pedicle was reported by Sacerdotti and Frattin¹⁸ in 1901. These observers described bone occurring in three of four rabbits from seventy-four to eighty-five days after ligation. In two cases the ureter was also included in the ligation. In one experiment at autopsy, some of the pelvis epithelium persisted, and bone formed in spite of the ligation of the ureter, in the other no bone was formed, and the pelvic epithelium had completely disappeared. Poscharissky⁴ found bone in three of five animals in which the renal vessels had been tied. Maximow¹⁹ found bone as early as five weeks after ligation of the renal pedicle and described the process in connection with his studies on histiogenesis of blood cells. Liek²⁰ confirmed the foregoing observations in a series of sixteen rabbits, in four of which he had made a high ligation of the ureters as well as of the vascular pedicle. No bone formed in the latter four. He stated that the necessary requirements for bone formation, namely young connective tissue near calcium deposits, were met following renal pedicle ligation and commented on the relation of the bone to the persisting pelvic epithelium but did not associate the two factors.

This problem has been studied in great detail from a histiogenetic standpoint by Asami and Dock²¹. All observers have noted that bone occurs in thin lamellae in the connective tissue immediately beneath the mucosa of the renal pelvis, and, if of any extent, is exactly parallel to it. It is never found in the scar tissue of the renal cortex, although calcification is constantly present in this location. All authors have stressed the concept of metaplasia of connective tissue into bone through some unknown influence. Asami and Dock concluded "that bone formation in the kidney with ligated pedicle takes place in three ways (a) through

18 Sacerdotti, C., and Frattin, G. Ueber die heteroplastische Knochenbildung. *Arch f path Anat u Physiol* **168** 431, 1902.

19 Maximow, A. Ueber experimentelle Erzeugung von Knochenmarks-Gewebe. Vorläufige Mitteilung, *Anat Anz* **28** 24, 1906.

20 Liek, E. Experimenteller Beitrag zur Frage der heteroplastischen Knochenbildung, *Arch f klin Chir* **80** 279, 1906, Ein weiterer Beitrag zur heteroplastischen Knochenbildung in Nieren, *ibid* **85** 118, 1908.

21 Asami, G., and Dock, W. Experimental Studies on Heteroplastic Bone Formation, *J Exper Med* **32** 745, 1920.

the activity of young fibroblasts which accumulate to form a membrane-like structure (resembling periosteum), (b) subsequently by direct ossification of hyaline connective tissue in continuity with prepared bone, (c) through erosion of lime plaques and laying down of lamellar bone by cells derived from fibroblasts (osteoblasts) "

Pearce²² observed bone formation following excision of the lower pole (approximately one-half) of the kidney with suture of the defect in six of nineteen kidneys. Bone developed in connection with epithelial buds of the pelvic mucosa. He commented "For this peculiar localization there is no explanation."

I have observed bone formation beneath the pelvic mucosa in two of three dogs forty days following fulguration of the renal pelvis with an electrical current of high frequency. This was observed once fifty-two days following the application of 95 per cent phenol.

Strauss²³ observed the formation of bone in experimental reconstruction of the ureter in dogs by means of a modified end to end suture of a pedicle flap consisting of the transversalis muscle, fascia and the peritoneum to the ends of the divided ureter. He stated that the peritoneum became replaced by transitional epithelium and the transversalis fascia by bone, and he thought that possibly the tissues became infiltrated with acid from the urine which caused sclerosis and was followed by bone formation.

BONE FORMATION IN THE URINARY BLADDER

Neuhof,²⁴ in a study of fascia transplantation into vesical defects in eighteen dogs, observed that bone constantly developed in the surface of the fascial patch bordering on the urine and was invariably confined to this fascia. His opinion was that bone formation could be explained only by a metaplasia of connective tissue, and that the genesis of this bone depended on the deposition of lime salts in the necrotic tissue of the fascial patch in contact with the urine. Apparently, he felt that an imbibition of calcium salts took place which stimulated the surrounding connective tissue to build up the most powerful barrier possible, that is, bone. Cartilage was found once in these experiments.

This experiment of Neuhof was repeated, and the observation of bone was confirmed by Phemister⁹ who extended his observations to

22 Pearce R. M. Notes on the Later Stages of the Repair of Kidney Tissue (Dog) with Special Reference to Proliferation of Pelvic Epithelium and Heteroplastic Bone Formation, *J. M. Research* **20** 53, 1909

23 Strauss, A. A. An Artificial Ureter Made from the Abdominal Wall *Surg. Gynec. Obst.* **18** 78, 1914

24 Neuhof H. Fascia Transplantation into Visceral Defects, *Surg. Gynec. Obst.* **24** 383, 1917

the rabbit and sheep, which are herbivorous animals with alkaline urine as opposed to the acid urine of the dog. In these animals the fascial patches in vesical defects did not ossify, and he felt that the acid reaction of the dog's urine had something to do with the formation of bone.

Concerning Neuhof's experimental observations, Leriche and Policard²⁵ commented "In certain places but on the bladder particularly, and constantly the aponeurotic graft gives rise to a plaque of true bone. It is easy to reconstruct the progress of these phenomena. In contact with the calcareous urine, the fascia necroses and is calcified. Around the borders of the old transplant, a proliferating tissue is formed. In proximity to a calcium collection, it ossifies. It is always the same fundamental process. And these experiments undertaken without preconceived ideas are a rigorous demonstration of the mechanism which we have advanced."

Thus it will be seen that certain clinical and experimental observations relative to the formation of bone in connection with the kidney pelvis, ureter and bladder have accumulated. The pathogenesis of this bone was unknown. The following experimental work was undertaken in an endeavor to throw some light on this phase of the subject as well as on the general subject of bone formation.

Axhausen²⁶ transplanted the gastric and vesical mucosa to the peritoneal cavity in sixteen dogs. The transplants were made to the outside of the stomach or bladder and lasted from fourteen to seventy days. At autopsy he described the formation of cysts lined by epithelium. The fluid in the cysts lined by mucosa of the bladder was dark red, sanguineous in color, as opposed to the light opalescent fluid in gastric cysts. Bone was apparently not observed, for it is not mentioned in this article.

EXPERIMENTAL OSTEOGENESIS

Dogs were used throughout the experiment, except when otherwise indicated. The surgical procedures were carried out under aseptic precautions, ether anesthesia being used. Whenever transplantation of tissue was done, this was autotransplantation. The animals were kept on a varied stock diet. The wounds were sutured with 00 white silk throughout.

EXPERIMENT 1—This was a critical experiment to ascertain whether the urine played a rôle in the formation of the bone in the fascial transplants to the bladder.

The abdomen was opened, both ureters were isolated and through a stab incision were transplanted to the skin in the groin just above the inguinal ligament.

²⁵ Leriche, R., and Policard, A. *The Normal and Pathological Physiology of Bone*, Translated by Moore and Keen, St. Louis, C. V. Mosby Company, 1928, p. 194.

²⁶ Axhausen. *Die freie Schleimhautüberpflanzung im Experiment*. *Arch. f. klin. Chir.* **102** 121, 1913.

The dome of the bladder was then opened and dried with gauze. A circular piece of fascia 2 cm in diameter from the anterior sheath of the rectus muscle was then sutured to the edges of the opening in the bladder with a continuous silk suture (fig 1).

After fifty-five days, the specimen was removed, and along the intravesical portion of the graft a dense button of bone was found strictly confined to the fascial transplant. The transplant was dimpled.

Microscopic examination (fig 2) showed that the surface of the fascial transplant was covered with the transitional epithelium of the bladder. Beneath the

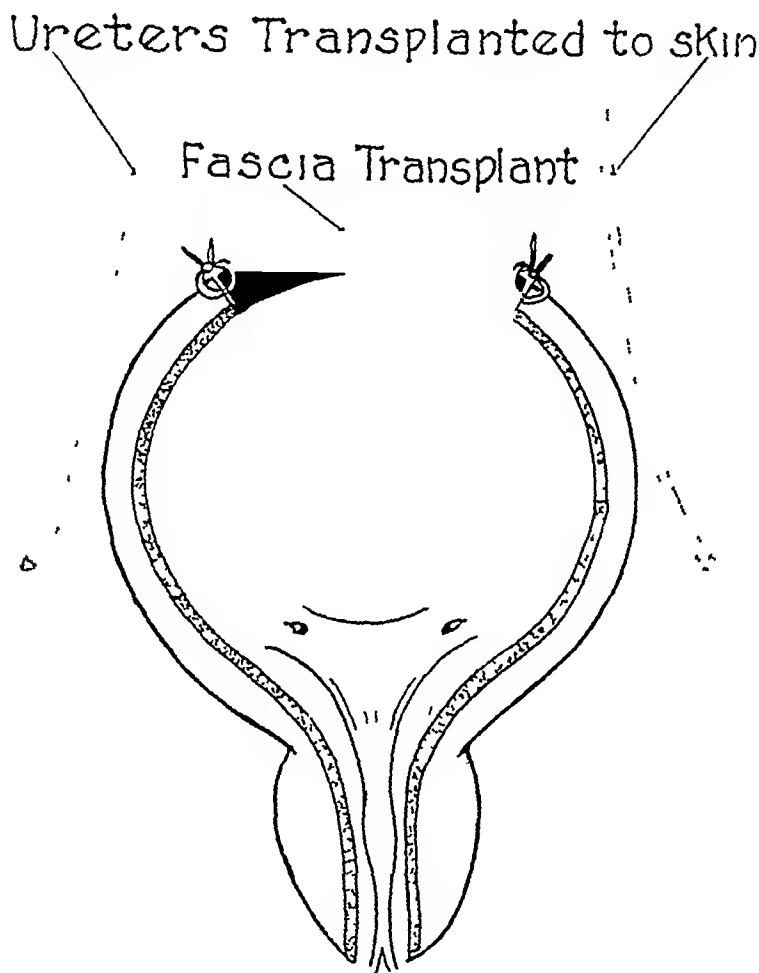


Fig 1—Diagram to illustrate experiment 1 in which following bilateral ureterocutaneous anastomosis, fascia was transplanted to the dome of the bladder.

epithelium, but separated from it by a small amount of areolar tissue, there was bone in parallel anastomosing plaques with haversian canals containing bone-marrow, connective tissue and blood vessels. On either side of the transplant at its junction with the wall of the bladder, there had been an ingrowth of epithelial cells in the form of finger-like processes continuous with the epithelial lining of the bladder and the transplant. In the transplant adjacent to these processes, in many places, there were islands of bone (fig 3), but in the wall of the bladder adjoining this epithelial invasion, there was no bone in any of the sections. This observation is of considerable importance, as will be seen subsequently. The bone



Fig 2 (dog 337) —Bilateral ureterocutaneous anastomosis, following which fascia was transplanted to bladder. Epithelium covers the transplant, beneath which there is bone formation. An epithelial downgrowth (A, A) is shown at the junctions of the musculature of the bladder and fascia transplant. Notice that bone (B) occurs only in the transplant. There is no bone on the bladder side of these epithelial processes.



Fig 3 (dog 337 sixty days experiment 1) —At the junction of the fascial transplant (I, I) and the wall of the bladder (B, B), an epithelial downgrowth (C) has occurred. Note that the bone (D) occurs only in the fascia and not on the bladder wall side or the epithelial process. $\times 110$

was covered with large numbers of the cells commonly called osteoblasts, indicating an advance in the osteogenetic process. Wherever there was an island of bone, there was an area of vesical epithelium in the immediate vicinity. However, the converse does not hold, for in some of the sections islands of epithelium were seen without accompanying bone.

This experiment was repeated in three dogs, with the same results, it established conclusively that urine is not a factor in the production of bone in this location.

EXPERIMENT 2—Since the urine is not a factor in the osteogenesis in fascial transplants to the urinary bladder, the bone must arise from some anatomic abnormality such as poor circulation or from the influence of some intrinsic element in the wall of the bladder acting on the connective tissue. This experiment was devised to attempt to determine which of these factors was responsible for the osteogenesis.

The abdomen was opened, and a circular area of the muscular coat of the bladder was removed intact by sharp dissection from the smooth glistening mucosa. When this had been done, the shining mucous membrane was moistened with saline, and the remaining filaments of cottony connective tissue were removed as far as possible. All this was done without opening the lumen of the bladder. The mucosa was then incised, and the area of denuded epithelium (2 cm in diameter) was excised and transplanted on the sheath of the right rectus abdominis muscle, where it was sutured in place with a continuous suture of silk. Similarly, on the sheath of the left rectus muscle the remaining elements of the wall of the bladder, free from epithelium, were sutured in place. The incision in the bladder was then sutured. After sixty days, the first animal was killed.

In the right rectus sheath, a cystic structure was found. The superficial aspect of the cyst was covered with bone, whereas the deep surface was soft, was free from bone, and fluctuation could be demonstrated. The cyst was opened, and 3 cc of blood-stained fluid was removed. Microscopic examination of the cyst (fig 4) showed it to be lined by transitional epithelium, histologically not different from that of the bladder. Surrounding one surface of the cyst (that nearest the skin), there was a plate of bone consisting of anastomosing plaques of living bone with fibrous and hemopoietic marrow in the haversian canals. At either end of the cyst (fig 5) there were finger-like projections of epithelium that were completely surrounded by bone.

In the left rectus sheath, no bone was found, and it was impossible to determine accurately the site of the transplant except by the presence of the silk sutures.

This experiment has been repeated forty-four times with essentially the same results. Bone is present in close relationship to the epithelium which has formed a cyst, the bone never completely surrounds the cyst (fig 4). The presence of epithelium is necessary for the formation of the bone. The bone in all these experiments formed superficial to the cyst. Bone never forms in association with the fibromuscular elements of the wall of the bladder and invariably forms in association with the epithelial transplants, provided the animal lives twenty days or more. In several instances, marked infection of the wound occurred, nevertheless small areas of bone could always be found on careful search. Of course if the infection were to destroy the entire graft, no bone would form, but this has never been observed. The vesical epithelium is particularly hardy and favorable for transplantation.

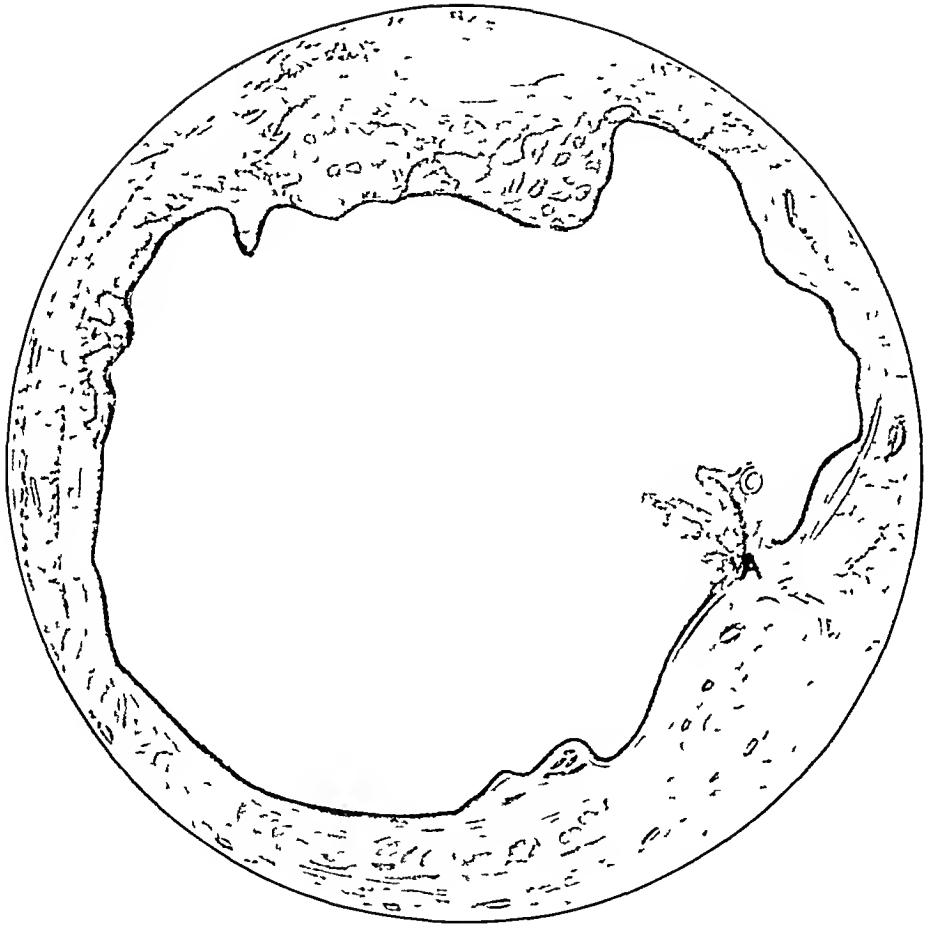


Fig 4—Camera lucida drawing of a cyst resulting from transplantation of the mucosa of the bladder in rectus sheath illustrating the extent of the bone (fifty-two days) Typical benign papilloma occurred three times in this series as at *A*



Fig 5 (dog 74)—Mucosa of bladder transplanted to rectus sheath (sixty-two days). Bone has formed around several islands of mucosa (*A*). The island of mucosa in the lower part of the section is entirely surrounded by bone, whereas the central ring of mucosa is only partly surrounded, $\times 65$

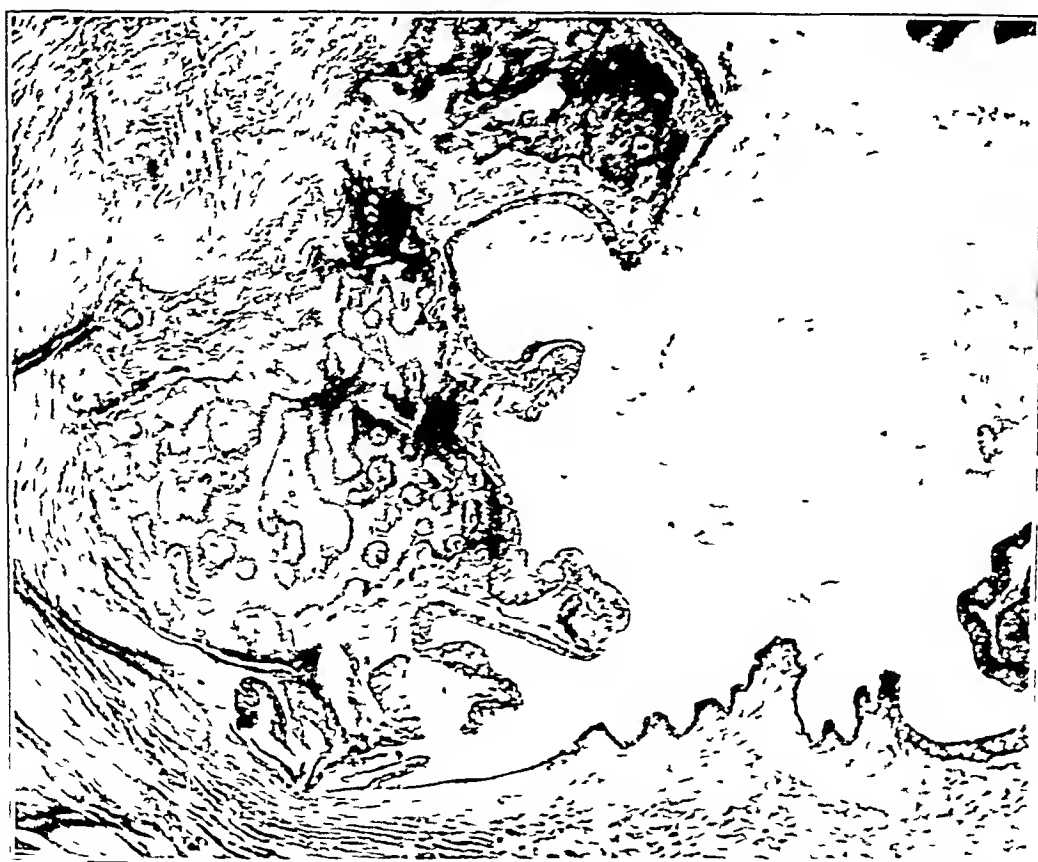


Fig 6 (dog 552)—Whole wall of bladder transplanted to rectus sheath (forty-five days). Epithelium, bone and fascia are shown below. The bone is closely adjacent to the newly formed epithelium. Note haversian canals and fibrous marrow.

EXPERIMENT 3—A brief outline of the histogenesis of bone derived from bladder transplants in connective tissues is given

In a series of eight dogs, a circular area of mucosa of the bladder was denuded of its muscular coat and transplanted as in experiment 2. The specimens were excised at various time intervals for microscopic examination.

At seven and nine days, the epithelium was seen to have formed an epithelial lined spheroid containing fluid (fig 8). The newly formed epithelium was considerably lower than the transplanted epithelium and consisted of a single or double layer of flat or cuboidal cells. At fourteen and sixteen days, the epithelium had formed its more characteristic appearance (fig 9), and it was difficult to



Fig 7 (dog 74)—Transplant of mucosa of bladder to rectus sheath (sixty-two days). Note relationship of epithelium (A) to bone. Haversian canal with hemopoietic marrow at B, $\times 160$.

differentiate between the newly formed epithelium and the transplanted mucosa. At this period the connective tissue surrounding a portion of the cyst appeared edematous, and under high magnifications the edema was fibrillary in type. This connective tissue was more eosinophilic and contained fewer nuclei than connective tissue surrounding other portions of the cyst and was presumably a pre-ossous stage in the process.

Nineteen days after the transplant, the first spicules of bone were seen adjacent to the newly formed mucosa. In all transplants older than this, bone was constantly found in connection with the epithelial transplants, and it reached its height about two months after the transplantation.



Fig 8 (dog 595)—Epithelial lined cyst resulting from transplantation of bladder to rectus sheath, nine days. The newly formed epithelium is included in the photograph, $\times 43$



Fig 9 (dog 689)—Mucosa of bladder transplanted. The fibrous tissue at A is edematous and eosinophilic greater than in the fibrous tissue elsewhere in the section. Pre

The bone showed little tendency to atrophy and had been observed persisting as late as three hundred and sixty days after the transplant. At this age, however, the bone is not greater in amount than at sixty days.

The bone is typically lamella membranous bone with haversian systems and contains bone-marrow.

EXPERIMENT 4—Can the location of the bone which forms around a part of the circumference of the cyst developing after a transplant of the mucosa of the bladder to rectus sheath be altered?

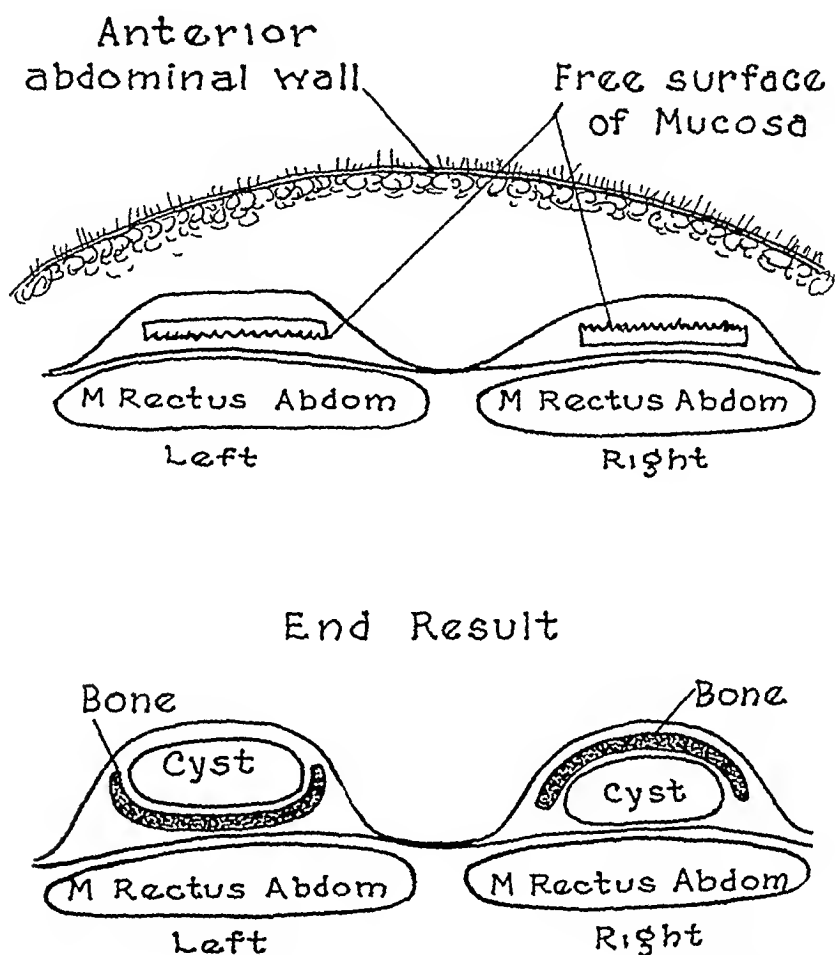


Fig 10—Diagram of experiment 4, with the result. Above the wall of the bladder has been transplanted on the left rectus muscle so that the free surface of the epithelium is toward the peritoneal cavity, whereas the mucosa of the bladder on the right, faces in the opposite direction toward the skin. Below, are illustrated the epithelial lined cysts which develop. The bone on the left is situated on the deeper aspect of the cyst, as opposed to the right where it is on its superficial aspect. Bone always forms in the region of the newly formed epithelium.

In this experiment mucosa of the bladder was transplanted to the sheath of the rectus muscle in two equal strips each about 2 cm in length. A strip was sewed in the right rectus sheath so that its free surface (intravesical portion) faced in the direction of the skin as in experiment 2. On the left rectus a strip was sewed in so that its deep surface faced the skin, and its free surface faced the peritoneal cavity (fig 10).

At the end of fifty days, the animal was killed. Each cyst was partly surrounded by bone. The cyst which had formed on the right rectus sheath had bone covering its superficial surface, whereas that which had formed on the left rectus sheath had bone covering its deep surface (that is in the direction of the peritoneal cavity). This experiment was repeated six times, with constant results. The bone formed always in the vicinity of the newly formed epithelium rather than about the transplanted mucosa.

EXPERIMENT 5—Can cysts lined by mucous membrane from the urinary bladder be developed which will be surrounded entirely by bone?

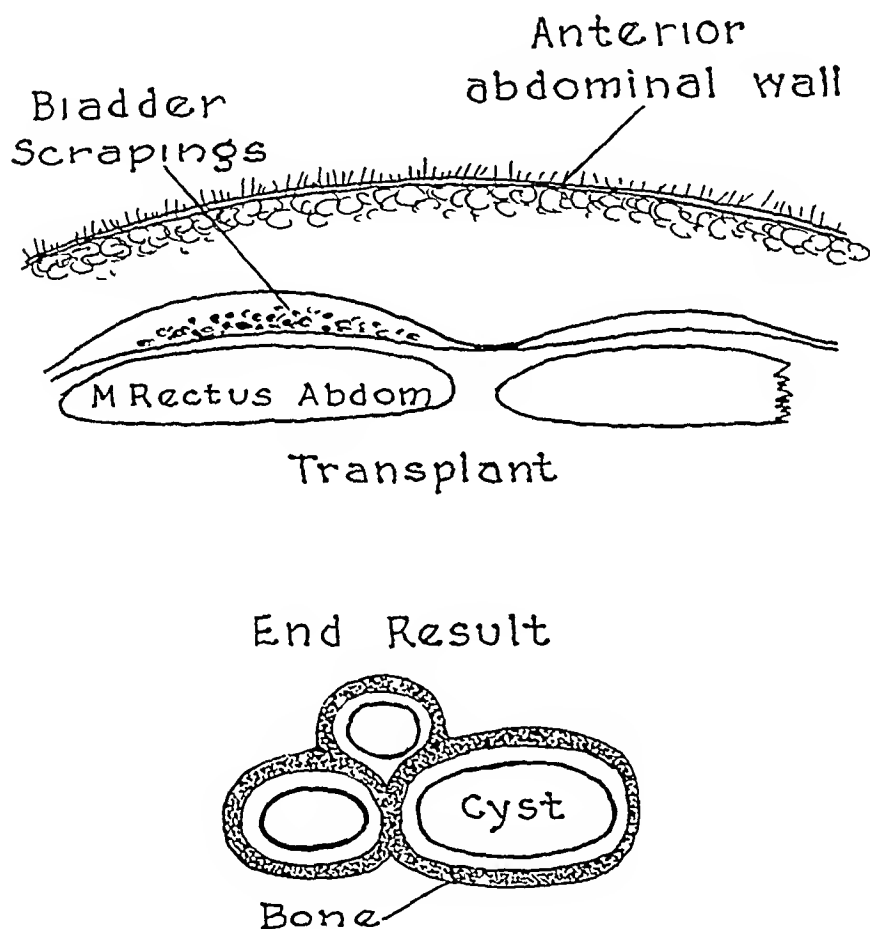


Fig 11—Diagram illustrating the deposition of scrapings of epithelium of bladder between the layers of the rectus sheath, below a type of multilocular cyst completely surrounded by bone, which resulted in one experiment at forty-nine days.

In this experiment the urinary bladder was opened through an incision in the vertex, the outer portion of the anterior sheath of the rectus abdominis was then split into its two component layers of fascia for a short distance. The mucous surface of the bladder was then lightly scraped with a sharp knife, and the blood-scrapings thus obtained were deposited in the connective tissue envelop (fig 11). About one half of the bladder was thus treated, and the hiatus in the rectus sheath was closed by suture. The bladder was then closed.

The dog was killed after forty-nine days, an ovoid multilocular cyst 2 by 2 cm had formed which was completely surrounded by bone (fig 12) The cyst was filled with a dark brown serosanguineous fluid

Microscopic examination showed that the mass was composed of two rather large cysts the bony walls of which were continuous In the bony walls of these large cysts there were numerous smaller cysts surrounded by bone (fig 13) All of these cysts were lined by the mucous membrane of the bladder, which in most places was much thinner than that found in the contracted bladder, as if the contained fluid had been under increased tension and had flattened the epithelium This experiment was repeated four times with similar results, except that the cysts were in no instance as large as in the original experiment Grossly, however



Fig 12 (dog 47, forty-nine days)—Anteroposterior and lateral roentgenogram of a cyst developed as in figure 11

the cysts derived from transplantation of scrapings from the bladder were entirely surrounded by bone in every instance, and the bone was in intimate association with the transplanted mucosa

The factor making for the formation of bone around the entire surface of the cyst seems to be the innumerable small scraping-grafts which must have assumed many different positions, allowing the osteogenetic effect of the proliferating mucosa of the bladder to act in many directions instead of in one as in the previous experiment, in other words, in this experiment there was far greater surface area of proliferating epithelial cells exposed to the fascia

EXPERIMENT 6—Transplantation of the ureter and kidney pelvis to the parietal fascia will produce epithelial-lined cysts partially surrounded by bone, but similar

transplantation of the cortex or medulla of the kidney or of the prostate does not lead to osteogenesis

1 The kidney and ureter of a dog were excised, through a median abdominal incision, and pockets were prepared in the fibrous sheath of the rectus abdominis muscle for (a) renal cortex, (b) renal medulla, (c) pelvis epithelium and (d) whole ureteral wall. All transplanted tissues were sewed in place by means of silk sutures. The fascia was then closed over these transplants.

After fifty days, the dog was killed and the specimens examined. As has been demonstrated by Didier and Guyon, the renal cortex and medulla did not lead to the formation of bone, the grafts entirely disappeared, and no vestige of them could be found.

The grafts of the renal pelvis and ureter behaved exactly like those from the epithelium of the bladder. Epithelial-lined cysts (figs 14, 15, 16) formed, surrounded in part by bone, the bone was located in the region of the newly formed

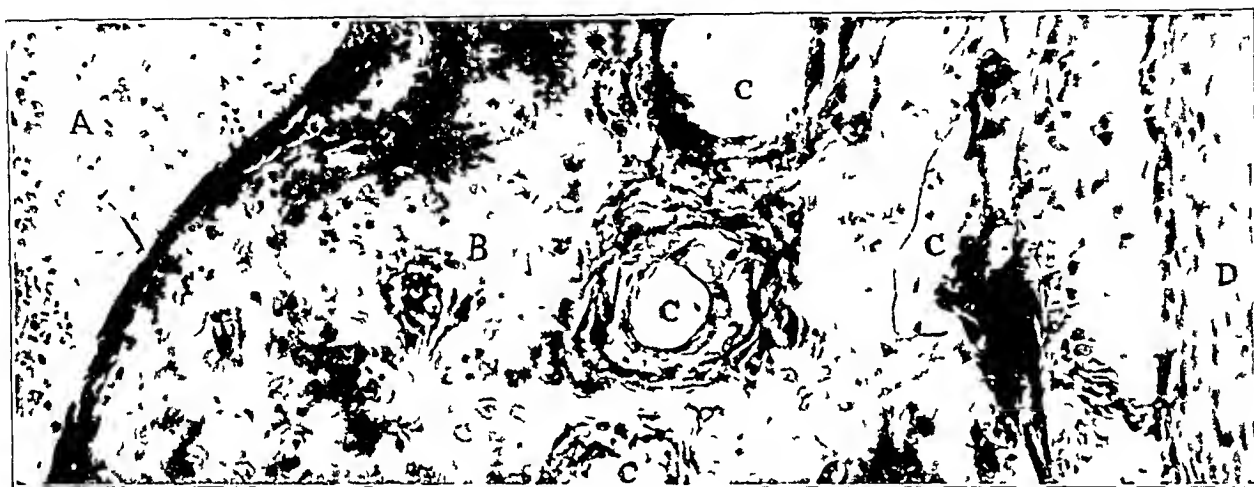


Fig 13 (dog 47) —Photomicrograph of a portion of a multilocular cyst (fig 12) entirely surrounded by bone resulting from transplantation of scrapings of bladder into rectus sheath (forty-nine days). A, sanguineous fluid in cyst, B, bone, C, smaller cysts in wall, and D, fibrous connective tissue of rectus sheath.

epithelium and was comparable in amount with the vesical grafts of the same age. This experiment was repeated and confirmed in two dogs.

2 In seven dogs the peritoneal cavity was opened through a right rectus incision extending almost to the pubic bone. The bladder was delivered, and the fatty tissue around the prostate was opened by blunt dissection. The prostate was thus exposed and a cuneiform area of prostatic tissue removed, care being taken not to open the urethra. The defect in the prostate was sutured with a continuous silk suture. The prostate graft was then treated in one of several ways: either transplantation in toto by suture to the split rectus sheath, or after moreellation with sand or by a sharp knife, the fragments were deposited in the fascia. The former method gave better results. The transplant was examined ten, fourteen, fifty-four and seventy-two days later. The prostatic tissue usually survived and grew (fig 17). Bone was not observed associated with prostatic transplants in any case.



Fig 14 (dog 505-L) —Transplant of mucosa of kidney pelvis to rectus sheath (fifty days) The same relationship of epithelium to bone exists, $\times 47$

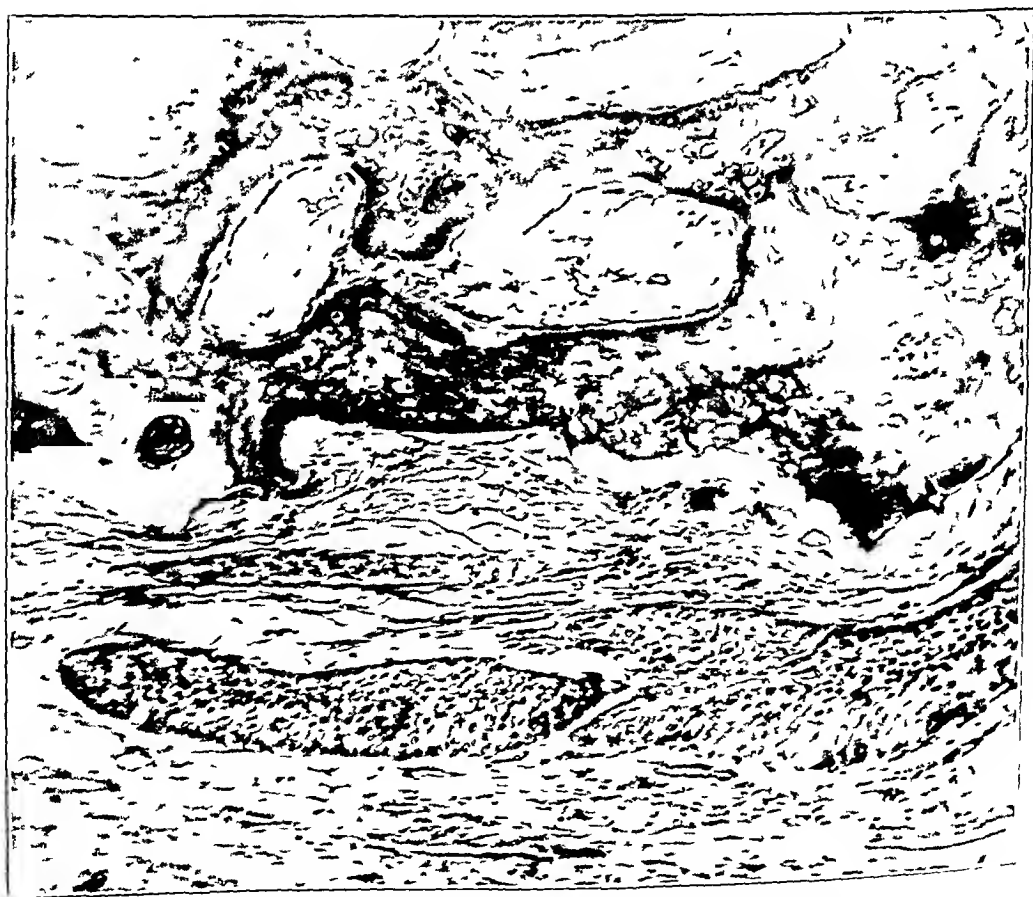


Fig 15—Higher magnification ($\times 130$) of figure 11



Fig 16 (dog 505-R) —Transplant of whole ureter wall to rectus sheath (fifty days) Typical membranous bone has formed Note relation of epithelium (A) to bone and that surface of bone is covered with osteoblasts, $\times 130$



Fig 17 (dog 691) —Transplant of prostate to rectus sheath seventy-two days The epithelium appears normal, there is no bone formation, $\times 155$

EXPERIMENT 7—Control experiments Epithelial transplants were made from the adrenal, gallbladder, stomach, jejunum and colon to the rectus sheath

The right adrenal gland was removed in three dogs and the cortex was divided into two portions, one of which was transplanted in a puncture wound of the right kidney and the other sewed in the sheath of the rectus abdominis Section at eighteen, twenty-two and thirty-five days demonstrated the survival of the graft by the presence of yellow tissue, microscopically composed of vacuolated cells arranged in cords No bone formed (fig 18)

Free transplants of the gastric mucosa in four dogs (fig 19), of the wall of the gall bladder in two and of the mucosa of the jejunum and colon in one dog,

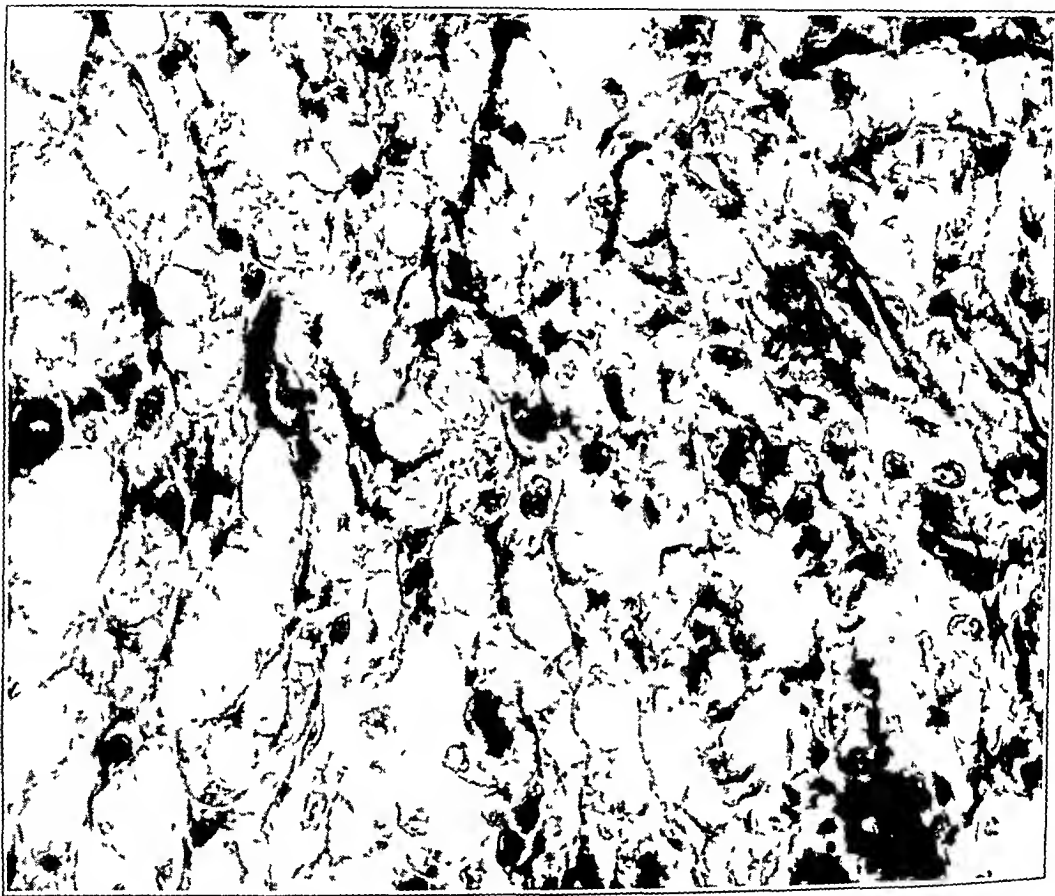


Fig 18 (dog 132)—Transplant of adrenal cortex to rectus sheath, twenty-two days The cortex has survived The cordlike arrangement of lipid containing vacuolated adrenal tissue is easily seen

to the abdominal fasciae failed to produce bone in any of the experiments Small epithelial-lined cysts containing cloudy fluid formed in every instance

A transplant of the dura mater which was obtained through the elevation of a button of the parietal bone by means of a crown trephine to the rectus sheath failed to cause the development of bone in two cases

In three instances, thin shavings of bone measuring about 1 by 1 by 0.2 cm were transplanted to the rectus sheath, these did not lead to osteogenesis The bone had disappeared in seventy days in two animals, and had diminished greatly in size in the third

A piece 2 cm square of the synovia of the knee joint, including the joint capsule, was transplanted to the rectus sheath in two animals, section at sixty days failed to reveal the presence of bone

The results of the experiments in which bone and periosteum were transplanted as a free graft to fibrous tissue are in accord with the work of Phemister²⁷ and others, and those of the experimental transplantation of gastric mucosa are somewhat similar to the experiments of Anhausen²⁸

EXPERIMENT 8—Further evidence indicating the necessity for a proliferating epithelium in the osteogenesis resulting from the influence of the mucosa of the bladder on connective tissue is given

The abdomen of a dog was opened and the bladder delivered from the wound With a sharp knife the muscularis and adventitia and peritoneal covering of the

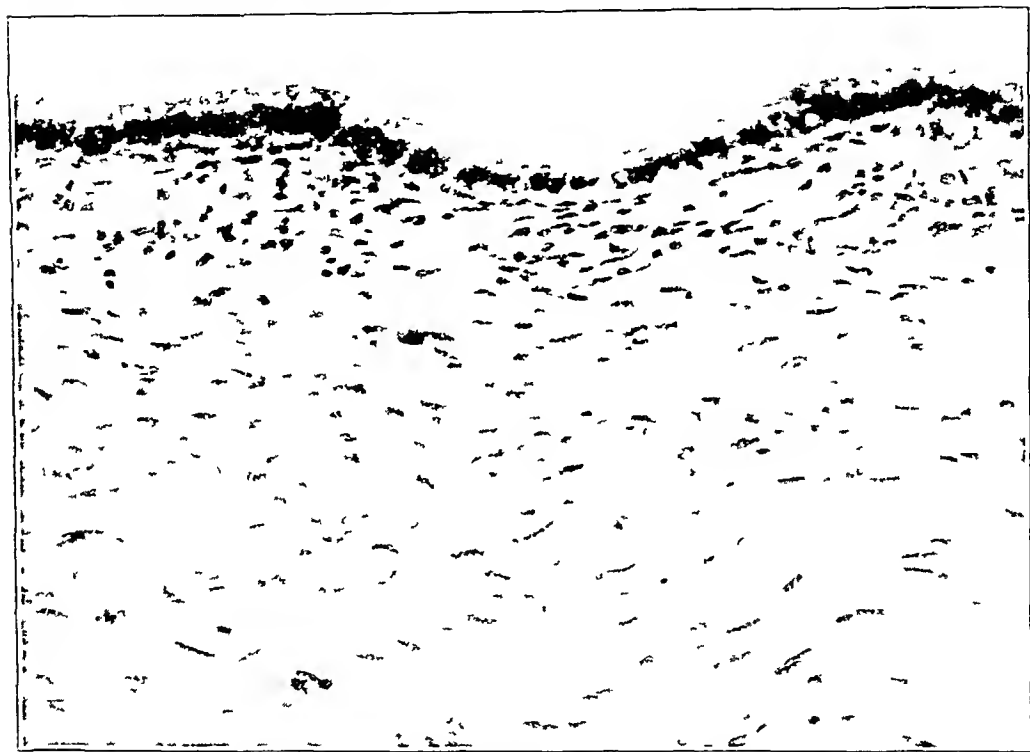


Fig 19 (dog 81)—Transplantation of gastric mucosa to rectus sheath, seventy-seven days, $\times 300$

bladder were removed in toto from a circular area of the wall of the bladder 2 cm in diameter, leaving the shining mucosa of the bladder unopened A piece of fascia from the rectus sheath was then secured to correspond with the excised portion of the wall of the bladder This fascia was sutured with silk to the adjacent muscular wall of the bladder to fill the defect (fig 20) After seventy-six days, the bladder was removed The transplanted fascia was recognizable by a slightly depressed dimpled area and by the silk sutures There was no formation of bone in this experiment or in five similar experiments lasting from forty-six to eighty-seven days

²⁷ Phemister, D B The Fate of Transplanted Bone and Regenerative Power of Its Various Constituents, *Surg Gynec Obst* **19** 303, 1914, Free Tissue Transplantations, *Surg Gynec Obst (Internat Abstracts Surg)* **18** 333, 1914

This experimental evidence indicates that a necessary requirement for bone formation is a proliferating epithelium or its products especially since it is known from experiment 4 that bone formed only adjacent to the newly formed epithelium

Comment—It seems established by these experiments that proliferating mucosa of the kidney pelvis, ureter and bladder has the power of exciting osteogenesis in the parietal fasciae, and that as far as the tissues described in the group of transplants reported in experiment 7 are concerned, it is a specific effect of the epithelium of the upper urinary tract

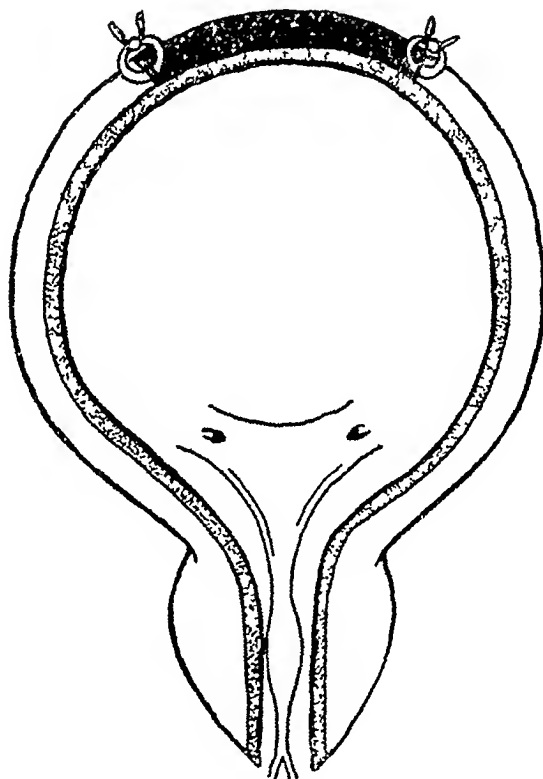


Fig 20—Diagram of experiment 8 The fibromuscular elements of a portion of the wall of the bladder have been renewed and replaced by fibrous tissue from the anterior sheath of the rectus The epithelium has not been opened

I shall next attempt to establish the fact that there are more factors concerned in this bone formation than proliferating mucosa of the urinary tract and any of the connective tissues and to present evidence that there is a difference between certain connective tissues, so far as they do or do not ossify under the influence of this proliferating epithelium

EXPERIMENT 9—The question to be answered by this experiment is whether the combination of proliferating vesical mucous membrane and connective tissue will always produce bone The experiment is described in two parts

1 A strip of mucous membrane of the bladder was excised and transplanted (*a*) in the rectus muscle four times, (*b*) on rectus sheath eighteen times, (*c*) in the subcutaneous fatty tissue three times, (*d*) on fascia lata twice and (*e*) on fascia covering the sacrospinalis muscle twice. The animals were killed after a period of from forty-nine to eighty-five days. In each instance, an epithelial-lined cyst developed surrounded in part by bone. The only variation in the results seemed to be quantitative, that is, when the transplant was made between fascial layers or in muscle tissue, more bone formed than when the transplant was made between fat and fibrous tissue or wholly within fatty tissue. This might be

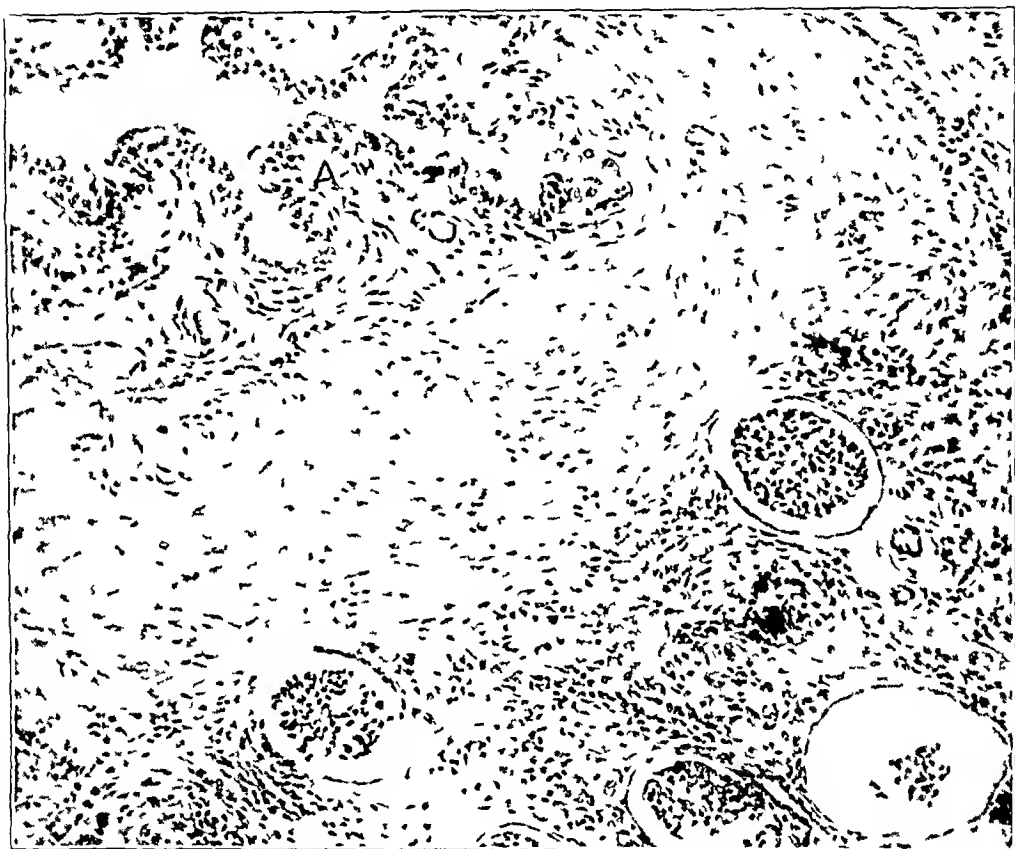


Fig 21 (dog 434) —Transplantation of mucosa of bladder to the kidney (cortex). A portion of the cyst lined by transitional epithelium which forms is shown at *A*. No bone results, $\times 130$

expected to have occurred, since there is less connective tissue in the subcutaneous fatty deposits than in the muscle or muscle sheaths.

A similar strip was inserted in the synovial cavity of the knee joint in three dogs and allowed to remain from forty-one to fifty days, the wound was closed in layers and a plaster cast was applied for ten days. The mucosa became attached to the synovial membrane forming a plaque of bone, near the patella, in two cases laterally and in the third medial to that sesamoid. At the conclusion of the experiment, a slight increase of synovial fluid was found. In no case were there loose bodies.

2 A strip of mucous membrane was excised from the bladder and placed in the parenchyma of (a) the kidney, (b) the liver, (c) the spleen and (d) the lung. Each experiment was done in three dogs.

The animals were killed from thirty-five to ninety-six days after the transplant was made. In no instance did bone develop.

In the lung, the transplant invariably became infected, and a chronic abscess of the lung was found at autopsy.

In the kidney, liver and spleen (figs 21, 22, 23) well formed epithelial lined cysts were found. Microscopic examination showed that the cysts were lined by transitional epithelium and had been surrounded by connective tissue. From his-



Fig 22 (dog 929) —Transplantation of mucosa of bladder to liver. An epithelial lined cyst (A) surrounded by connective tissue forms but no bone. $\times 90$

tologic evidence, it was impossible to see any difference in either the epithelium or the connective tissue, and in cysts of the same age in the sheath of the rectus. Here obviously the difference between bone formation in these parietal connective tissues and its absence in the organs mentioned must lie in a chemical or physical difference in the connective tissues, since the epithelium and the morphologic appearance of the fibroblasts are the same.

EXPERIMENT 10—Since it has been reported that transplants of connective tissue to the dome of the bladder in the rabbit will not ossify (Phemister⁹), the question arose whether free transplants of mucosa of the bladder into fascia will form bone in this animal.

In six rabbits the urinary bladder was opened and the dome excised, the bladder was then closed by a continuous Lembert suture, followed by a purse-string suture which held in place the inverted dome of the bladder. The excised dome of the bladder was then sewed in the sheath of the rectus abdominis muscle with silk. In two of the animals infection followed operation, and here a tumor the size of a hen's egg was palpable beneath the skin. One of these animals was killed at the end of thirty days and the other after a hundred and forty-five days. Necropsy showed the tumor to be composed of a dense mass of yellow caseous tissue, thoroughly inspissated, from which bacteriologic examination showed *B subtilis* in almost pure culture. In the animal killed after one hundred and forty-



Fig 23 (dog 10) —Bladder epithelial transplant to spleen. The epithelium (A) is surrounded by connective tissue, but no bone has formed, $\times 55$

five days, the wall was calcified. There was no evidence of the mucosa of the bladder in either experiment. The tumors were chronic pyogenic abscesses. The remaining four animals were killed after sixty, seventy-one, eighty-four and ninety-five days. All the experiments were negative for bone except that lasting ninety-five days. In each a cyst was found lined by epithelium of the bladder containing fluid and surrounded by connective tissue. In the animal killed after ninety-five days, a plaque of bone 1 cm in diameter was found adjacent to the vesical mucosa in the rectus sheath resembling the observations on the dog.

EXPERIMENT 11—Since the mucosa of the bladder of the rabbit forms bone only under exceptional circumstances when transplanted to the rectus fascia, is the failure of bone deposition a local or a general process? Experiment 10 was

repeated with the addition of the administration of large doses of viosterol or of parathormone

Seven rabbits were operated on as in the last experiment. From three to six days later, viosterol in oil 1,000 D, was given to the rabbits in doses of 2 cc daily by stomach tube. This was given every second day.

One rabbit died after three doses and one after five doses. The remaining rabbits were given between eight and fifteen doses. Necropsy after from thirty-five to forty-nine days revealed the usual observations of massive doses of viosterol in rabbits, such as a marked deposition of calcium in the aorta and somewhat less in the kidney and other organs. The usual epithelial-lined cysts were found, but bone was not present. It is interesting that necropsies of the animals four and five months after the feedings with viosterol were stopped showed virtually no regression in the calcification in the aorta.

Two rabbits were similarly treated, except that six units of parathormone given subcutaneously every second day was substituted for the viosterol over a period of thirty days. Three rabbits were similarly treated, except that eight units of parathormone was administered every second day for ninety-eight days.

Autopsy of the five rabbits showed well formed cysts lined by mucosa of the bladder and containing the usual sanguineous fluid in four, in the fifth no trace of the transplant could be found (infection?). No bone was found in any of the experiments. Thus the agents that will cause the deposition of bone in man or rickets produced experimentally or that will normally raise the blood calcium did not induce ossification, this is interpreted as evidence that in the rabbit the failure of the epithelium to stimulate bone formation in the rectus sheath is due to local conditions in either the epithelium or the rectus sheath rather than to general causes such as a lack of vitamin D or hypocalcemia.

It is known from the earlier observations in the literature²⁸ that under certain conditions bone forms in the urinary tract of rabbits (and my work would suggest strongly that it is due to the action of the proliferating pelvic mucosa) as well as in the single instance cited in experiment 10. Therefore it would seem as if the rectus fascia of the rabbit were lacking in the attributes necessary for bone formation when epithelium of the urinary tract is transplanted to it.

EXPERIMENT 12—If the epithelium of the bladder influences at times the laying down of bone in certain connective tissues, why is bone a rare observation in the bladder itself where proliferating, epithelial processes are common as a result of infection, stone, operations, etc.?

In three dogs, the bladder was opened through an incision in the vertex. With a knife, the mucosa of the bladder was dissected from the parietal tissues. This is technically an easy procedure. The musculature of the bladder was thus denuded of epithelium except for a triangular area in the trigone and an irregular ring around the urethrovesical junction. Hemostasis was secured by the aid of a hot gauze pack inserted in the bladder and pressure from without on the pack. After hemostasis was complete, the incision in the dome of the bladder was sewed with two rows of silk, with care not to encroach on the denuded muscularis more than was necessary. In one of the animals it was found that a sheet of mucosa 8 by 5 cm. had been thus removed and in the others relatively large areas. These animals were killed after eighteen, thirty-five and forty-one days.

It was interesting to observe that the musculature of the bladder denuded in this manner was competent to prevent leakage into the peritoneal cavity. At thirty-five and forty-one days it was found that the epithelium (figs 24 and 25)

²⁸ Poschariskv (footnote 2, first reference) Sacerdotti and Frattin (footnote 18) Maximow (footnote 19)

had completely regenerated, lining the bladder. The wall was considerably thicker than normal, and distention was limited. The macroscopic and microscopic studies will be presented elsewhere. It is sufficient to state here that bone did not form in the wall of the bladder which is probably in a similar class with the other tissues that do not ossify under the influence of proliferating mucosa of the bladder.

Comment—It will be seen that there are apparently two classes of fibrocytes which react differently to the presence of adjacent proliferat-



Fig 24 (dog 546) —The mucosa was cleanly removed from the bladder except a small strip at the base, and bladder incision closed. The regeneration of the transitional epithelium is shown (forty-one days). An hypertrophied fibrous tela submucosa has formed limiting distention of the bladder. No bone formation, $\times 55$.

ing epithelium of the bladder, one which is susceptible of being ossified and the other which is not. In the first class (ossifying), are the connective tissues of the fatty-fibrous subcutaneous tissue, of striated muscle, of the fasciae (rectus sheath, fascia lata, fascia covering

sacrospinalis muscle) and capsule of the knee joint in the dog and the fibrous tissue that forms beneath the proliferating pelvic epithelium after ligation of the renal vessels in the rabbit

In the second class (nonossifying) are the fibromuscular wall of the urinary bladder and connective tissue stroma surrounding transplants of mucosa of the bladder in the liver, spleen and kidney in the dog and the fascia of the rectus sheath and the fascia lata in the rabbit

The physiologic difference between these fibroblasts which under the microscope seem identical is not apparent but it seems clear that such a difference exists

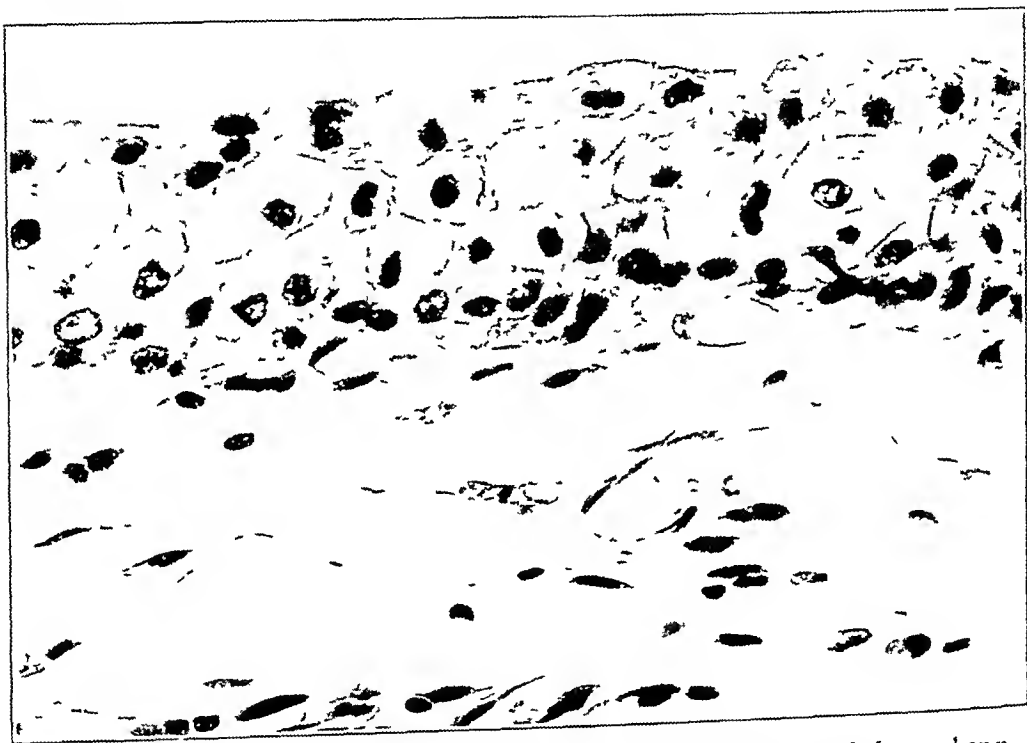


Fig 25 (dog 546) —Higher magnification of regenerated epithelium shown in figure 21 $\times 560$

EXPERIMENT 13 —Will fascia introduced into the fluid contained in cystic epithelial transplants of bladder to rectus sheath, in part surrounded by bone, ossify?

The result of this experiment are incomplete. Five experiments have been conducted as follows. A circular area of mucosa of the bladder 2 cm in diameter was excised and transplanted between the internal and external oblique muscles after bone had formed as determined by palpation through the skin, a second incision was made exposing the cyst, which was entered through a small incision in its surface that was not surrounded by bone. A small piece of fascia was then excised from the rectus sheath and inserted in the lumen of the cyst, the wall of which was then closed by a silk suture.

In dog 212, the original transplant to the rectus sheath was made on Oct 30, 1928. An easily palpable plaque of bone about 3 cm in diameter formed around the cyst. A small piece of fascia was inserted in the cyst two hundred and ninety-

eight days later. Examination forty-seven days after this second operation showed an irregularly spherical mass of bone about 4 mm in diameter lying free in the cyst fluid. Gross examination showed that the mass consisted of a shell of bone completely surrounding a core of fibrous tissue. Microscopic examination demonstrated the fibrous tissue core as living and surrounded by true bone. The bone, however, was lamellar with haversian system. The microscopic appearance of the bone (fig 26) is thus different from areas of bone known to be growing in 'tissue



Fig 26 (dog 212) —Roentgenogram and photomicrograph of bone which formed around a piece of connective tissue inserted in the fluid of an epithelial cyst caused by the transplant to mucosa of bladder and rectus sheath. Judging from the cancellous spaces, the fibrous tissue had become attached to the epithelial wall, although at autopsy the bone was found free as a loose body

culture," such as the osteocartilaginous loose bodies sometimes observed lying free in joints in man, which are known to be growing free in the synovial fluid. However, the presence of the loose body of bone with a central core of fibrous tissue would strongly suggest that the introduction of the fibrous tissue played a part in the formation of this shell of bone, it probably became attached to the wall in some way, later coming loose after bone had formed.

In two other animals, at necropsy thirty-one and thirty-seven days after the introduction of fascia, the fascia was found intact but not viable and not surrounded by bone. In two animals at necropsy forty-one and ninety-three days after this procedure, no fascia was found.

EXPERIMENT 14—Will the introduction of a silk suture in the lumen of an epithelial-lined cyst of the mucosa of the bladder lead to the deposition of salts on it as frequently occurs around nonabsorbable sutures in the lumen of the bladder?

The presence of stone around a silk or linen suture in the bladder is an extremely common experimental and clinical observation. It was with some interest, therefore, that a piece of sterile silk 3 cm in length was introduced as a loose body into the fluid secreted by the vesical epithelium in these cysts partly surrounded by bone. It was done three times, and the experiment was allowed to run thirty, thirty-seven and forty-seven days.

Examination in the thirty and forty-seven day experiments showed that a part of the thread had become surrounded by bone in the wall of the cyst to which it was attached. In the thirty-seven day experiment the entire thread was found lying free in the lumen of the cyst, as a part had been in the first two animals. In no case had gross precipitation of calcium salts occurred on the threads.

EXPERIMENT 15—This experiment was a study of the fluid in epithelial-lined cysts resulting from transplantation of the mucosa of the bladder to the sheath of the rectus abdominis muscle, especially of the calcium and phosphorus content (The chemical determinations were made by Dr. E. L. Compere.)

When a circular area of the wall of the bladder 2 cm in diameter is transplanted to the rectus sheath, a cyst forms containing a dark brown, sanguineous fluid, which does not clot spontaneously in three hours. Microscopic examination shows it to be made up chiefly of erythrocytes in various stages of degeneration, with a few leukocytes and desquamated epithelial cells. The amount of the fluid is rarely more than 4 cc, usually about 2 cc.

It seemed of interest to determine the calcium and inorganic phosphate content of this fluid and to compare the results with similar simultaneous determinations on the blood serum. In addition, in some experiments the hydrogen ion concentration and the carbon dioxide content of the fluids were determined.

The fluid was aspirated through the skin with an 18 gage needle and drawn under oil. Calcium was determined by the Collip²⁹ modification of the Kramer and Tisdall³⁰ method in most instances. In three of the determinations, the organic material was destroyed by heating with concentrated sulphuric acid before using the foregoing method, with approximately the same results. Inorganic phosphates were determined by the method of Fiske and Subbarow.³¹ The carbon dioxide content of the serum and cyst fluid was determined by the manometric method of Van Slyke and Neill.³² The bicolorimetric method introduced by Myers³³ and Hastings³⁴ was used for the hydrogen ion concentration.

29 Clarke and Collip. *J Biol Chem* **63** 461, 1925.

30 Kramer and Tisdall. *J Biol Chem* **47** 475, 1921.

31 Fiske and Subbarow. *J Biol Chem* **66** 375, 1925.

32 Van Slyke and Neill. *J Biol Chem* **61** 523, 1924.

33 Myers. *J Biol Chem* **54** 675, 1922. Myers, Schnitz and Booher. *J Biol Chem* **57** 209, 1923.

34 Hastings and Sendroy. *J Biol Chem* **61** 695, 1924.

The results are tabulated in table 1. In ten of thirteen determinations, the calcium was decidedly elevated above the blood serum calcium. In five of eight determinations, the inorganic phosphate content of the cyst fluid was markedly increased over the values for blood serum. In eight of nine determinations, the cyst fluid was more acid than the

TABLE 1—*Hydrogen Ion Concentration, Calcium and Phosphorus Content of the Fluid Found in Epithelial Lined Cysts of the Bladder Mucosa (Experiment 15) as Compared with Similar Values of Blood Serum in the Dog*

Dog No	Date	Days Transp	Cyst Fluid					Blood Serum				Ossification in Cyst
			Cc of Fluid	Ca*	P*	CO ₂ †	p _H	Ca*	P*	CO ₂ †	p _H	
256	9/10/29	62	3 0	15 9	11 0	6 32	10 4	5 16	43 16	7 51	---++	
212	9/10/29	47	3 6	15 6	9 6	6 45	10 98	3 44	49 2	7 57	---++	
215	9/14/29	80	5 4	10 77	8 23	6 35	10 77	4 91		7 43	---++	
543	11/18/29	29	2 6	13 35		7 35	10 34			7 42	---++	
543	12/18/29	59	10 0	10 72	5 9	6 97	11 07	5 33		7 53	Cyst fluid contains pus	
689	2/ 3/30	33	2 2		16 4	7 27	11 6	5 3	45 3	7 44	---++	
724	2/ 3/30	37	5 0		18 3	7 02	10 8	5 71	51 5	7 45	---++	
986	2/ 3/30	35	9 0	11 04	4 4	28 6	7 17	11 2	5 16	51 3	7 44	---++
821	3/10/30	62	0 5	16 3			11 6	6 15				---++
986	3/10/30	69	0 8	15 2			11 6	6 2				---++
928	2/ 3/30	100	6 0		114 7	7 69	12 20	6 66	55 9	6 92	---Cyst grossly infected	
873}	3/10/30	49}	0 65	17 4			11 86	6 25			---++	
506}		62}										
212	6/24/29	267	3 0	23 5			10 5				---++	
821	4/16/30	113	1 5	18 2	5 22		12 6	6 67			---++	
689	4/16/30	118	1 8	16 6	3 0		12 6	6 67			---++	
869	4/11/30	67	2 4	16 0	16 8		10 46	6 4			---++	

* Milligrams for each 100 cc

† Carbon dioxide content per cent by volume

TABLE 2—*Hydrogen Ion Concentration and Phosphorus Content of the Blood Found in Cysts of the Bladder Mucosa in the Rabbit, as Compared with Blood Serum (Experiment 15)*

Rabbit No	Date	Days Transp	Cyst Fluid					Blood Serum				Ossifica- tion in Cyst
			Cc of fluid	Ca*	P*	CO ₂ †	p _H	Ca*	P*	CO ₂ †	p _H	
348	12/30/29	50	0.75		7.16		7.32		7.02		7.35	No ossi- fication
353	12/30/29	50	0.6		7.4		7.34		6.7		7.39	No ossi- fication
362	12/30/29	50	1.0		6.7		7.35		7.04		7.34	No ossi- fication

* Milligrams for each 100 cc

† Carbon dioxide content per cent by volume

blood serum. The carbon dioxide content of the cyst fluid was much less in three of four determinations than the normal values obtained at the same time from the blood serum.

In three rabbits the phosphorus content and the hydrogen ion concentration of the blood serum and of the fluid of the bladder cyst were determined. Table 2 shows the results in tabular form. The phosphorus content and p_H did not vary strikingly from the values for blood serum.

In all of these determinations it must be realized that small amounts of fluid were necessarily used, so that the possibility of error is greater than if larger amounts could have been obtained. In three transplants in dogs, large amounts of fluid were obtained, these cases were probably not true cysts lined by transitional epithelium, but abscesses, since gross pus was seen. However, in each of the abscesses bone was found, but in two cases it was small in amount, this showed that the graft had apparently survived, at least in part. Ruling out these cases of gross infection, it will be seen that in the remaining cases the calcium content of the cyst fluid was markedly elevated above the value for serum calcium.

COMMENT

The proliferating mucosa of the kidney, ureter and bladder is a sufficiently strong stimulus to certain connective tissues in the dog and rabbit to induce the formation of bone. Certain other fibrocytes do not react in this way. The exact physicochemical change thus affecting the fibrocyte is unknown, as well as the mechanism of resistance to bone formation on the part of tissues in which bone does not form.

It seems logical, since the cyst fluid in most cases contained much more calcium and phosphorus than did the blood serum, to assume that this has a bearing on the problem especially since in certain cases, as in experiment 1, a cyst did not form, and the fluid secreted by the cells must have been disposed of in the tissues themselves. It must be granted as proved that the mucosa of the bladder in this position secreted³⁵ calcium and phosphorus into the lumen of the cyst.

It is possible that the newly formed epithelium, lining the cysts which form when mucosa of the urinary tract is transplanted to the rectus sheath in the dog, is more permeable to the fluid secreted by the epithelium than the older mucosa. This would explain the occurrence of the bone in the vicinity of the proliferating epithelium.

Since this osteogenesis occurs invariably (barring severe infection), this method affords a way of studying osteogenesis that offers certain advantages over that of osteogenesis from preexisting bone, periosteum or cartilage. The exact duration of the osteogenic stimulus is known in this experiment. Moreover, a fluid is present which may aid in the study of osteogenesis.

The production of bone under the direct influence of epithelial cells is proved for the first time by the experimental method. The observation of epithelial cells infiltrating bone is common in certain osteoplastic processes in the skeleton resulting from tumor invasion. This is frequently seen in man in the metastases of prostatic carcinoma to bone.

³⁵ Further unpublished studies by F. H. Entz in this laboratory indicate that the mucosa of the bladder normally secretes calcium and phosphorus.

and is seen in the hyperostosis overlying cranial meningiomas,³⁶ as well as in other tumors

Two views have been expressed regarding the pathogenesis of the bone in tumor metastasis. Von Recklinghausen and others explained this process as due to a stimulation of new bone by passive hyperemia due to venous obstruction by tumor cells. The second view has been advocated by Axhausen and others who believe that the new bone forms as a result of stimulation of the surrounding osteogenic elements by chemical substances formed by the tumor cells.

These experiments, which demonstrate a direct relationship between osteogenesis and certain epithelia, favor the second hypothesis, especially for metastases of carcinoma from the prostate, because of the ontogenetic relationship of the prostate to the urinary tract. Osteogenesis, however, has not occurred about prostatic transplants. It is possible that the reason for the failure of prostatic epithelium to stimulate bone formation in connective tissues is the difficulty in dissociation of the epithelium from its stroma, and it is known that the stroma of the bladder will not ossify in the presence of regenerating epithelium of the bladder.

This study indicates also the nonspecificity of periosteum and the osteoblast and that certain other connective tissues under an altered environment may acquire osteogenic properties.

SUMMARY

- 1 The direct influence of certain epithelial cells on connective tissue stimulating bone formation in it is shown experimentally.

- 2 Bone forms in a fascial transplant to the bladder of the dog in which the urine has been diverted. It is in close relationship to the epithelium and occurs only in the transplant.

- 3 Bone forms around a transplant of bladder, ureter and renal pelvis epithelium to certain parietal fascias (rectus sheath, fascia lata, subcutaneous tissue) and to muscle and synovial membrane in the dog. This is true spongy bone with haversian canals containing fibrous and hemopoietic bone-marrow.

- 4 These fibrocytes can be differentiated functionally from other fibrocytes (those which form around an epithelial transplant from the urinary tract into the kidney, liver and spleen, and those forming from the connective tissue of the wall bladder) which appear anatomically similar but do not participate in the formation of bone.

- 5 Transplants of the epithelium of the bladder to the sheath of the rectus abdominis fascia in the rabbit did not lead to bone formation.

³⁶ For a complete description of this process, see Phemister, D. B. The Nature of Cranial Hyperostosis Overlying Endothelioma of the Meninges, *Arch Surg* 6:554 (March) 1923.

except in one animal. This fascia also therefore can be differentiated from the connective tissue about the renal pelvis, which after ligation of the renal vessels proliferates and forms new bone. Viosterol and parathormone do not aid in ossification in epithelial transplants to the rectus sheath in rabbits.

6 It is the newly formed epithelium and not the nonproliferating part of the transplant that is the essential factor in this osteogenesis.

7 A secretion of fluid containing a relatively large amount of calcium and phosphorus occurs into epithelial-lined cysts of the mucosa of the bladder in the rectus sheath of the dog. It is a probable factor in bone formation.

8 Osteogenesis does not occur following similar transplantation of gallbladder, gastric, jejunal and prostatic epithelium into fascia.

9 Since the osteogenetic power of the mucosa of the renal pelvis has been demonstrated, it is most probable that this is the factor causing bone formation after ligation of the renal pedicle in the rabbit's kidney, especially since this rarely occurs following ligation of the ureter.

THE ASSOCIATION OF RAYNAUD'S DISEASE WITH CEREBRAL SYMPTOMS

REPORT OF A CASE WITH MIGRAINE, PSYCHONEUROTIC SYMPTOMS,
TRANSIENT HEMIPLEGIA AND DEATH¹

LOUIS CARP, M D

NEW YORK

In 1862, Raynaud¹ described the disease which bears his name. It is characterized by attacks of vasomotor and trophic disturbances in which local syncope (blanching) may be followed by local asphyxia (cyanosis) in peripheral portions of the body which may or may not be symmetrical. Paresthesias usually accompany these symptoms and signs. Despite the lack of vascular occlusion, peripheral gangrene is common. The disease is more frequent in neuropathic young women than in men. In a carefully studied history, psychic trauma or prolonged exposure to cold often suggests a not improbable etiologic influence. The symptom-complex, with varying characteristics, may continue intermittently over a number of years. According to Raynaud¹ and Buerger,² mild sensory disturbances are usually present, and hemoglobinuria, arthropathies and cerebral symptoms are sometimes observed. Differential diagnosis, not infrequently difficult, is also classified by Buerger.² In this paper the cerebral phenomena of Raynaud's disease will be considered.

Based on a review of the literature, the cerebral symptoms associated with Raynaud's disease may, in the main, be divided into the following groups: (1) central vascular manifestations—vertigo, headache, unconsciousness, aphasia, paralysis, convulsive seizures, etc.; (2) mental manifestations—psychoses and psychoneuroses of various types.

The following case, referred to me by Dr. N. E. Biodei for surgical opinion, is reported in order to bring out the association of psychic symptoms, attacks of migraine and transitory hemiplegia in a patient in whom a clinical diagnosis of Raynaud's disease was made.

REPORT OF CASE

History—G. S., aged 26, single, a Jew, who was born in Austria but who had lived in the United States twenty-three years, in the advertising business, presented himself on June 19, 1929, with the following history. The chief complaint

* Submitted for publication, Sept. 23, 1930.

1 Raynaud, A. G. Maurice. *De l'asphyxie locale et de la gangrene symétrique des extrémités*, Thèse, Paris, 1862.

2 Buerger, Leo. *The Circulatory Disturbances of the Extremities*. Philadelphia: W. B. Saunders Company, 1924.

was pain at the tip of the right index finger of eight weeks' duration. His father died at 62 of arteriosclerosis, his mother was diabetic and neurotic, two brothers and one sister were in good health and another sister had myxedema. The patient had had measles at 4, he had fallen, hitting the back of his head ten years before presentation. He attributed a partial loss of vision in his left eye, which had developed six years before, to this accident. At this time he was seen by Dr Ernst Waldstein, who found a slight myopia of the right eye and an old detachment of the lower half of the retina of the left eye. In October, 1925, and January, 1929, Dr Waldstein found the ocular picture unchanged. He had a fairly constant dry (cigaret?) cough for about three years, with frequent pains in the chest following exposure to cold. There was no fever. It is of interest that ten years before he fainted momentarily while walking in the street. He had always been very nervous.

He said that he had never had a venereal disease. He was a heavy cigaret smoker, and since his present trouble began had smoked about thirty cigarets a day. He indulged moderately in tea and coffee, but abstained from alcohol and drugs. In the past year he had shown a definite decline in business capacity.

The present illness began three or four months before he consulted me, when the patient noticed occasional blueness and coldness in the tip of his right index finger. About eight weeks before, he was bitten on the tip of this finger by a child. Soon afterward he began to have pain, swelling and tenderness in this region, for which he used hot soaks and ointments, without relief. About a week before I saw him his family physician removed the distal third of his nail, and a few days later he went to the Vanderbilt Clinic, where, under block anesthesia, the remainder of the nail was removed. It was found to be brownish and loose, and in the subungual space there were dark, unhealthy granulations and some dark blood, but no pus. The next day the intern noted clotted dark blood at the end of the finger. The roentgenogram showed no involvement of the bone. At my office two days later, the following additional history was obtained. The pain in his finger was becoming more intense, and it seemed to spread to his right hand and forearm. It became almost unbearable at night. Dependent position of the right upper extremity seemed to relieve the pain, but after this position was assumed for some time the distal part of the extremity became swollen. There was no fever or chills. He complained especially of temporal headaches on the right side which were quite severe, and which had shown remissions in the past three years. He became depressed and introspective, he had been worried about the future for some time, because he could not seem to get into his occupational stride. He had tried hard to combat a tendency to neuroticism, and he felt that he was becoming a financial burden to his family.

Examination and Course—The patient was in great pain. On the dorsal distal, phalangeal region of the right index finger, in the region of the nail bed there was a dark, bloody, sluggish, granulating area extending underneath the eponychium, the paronychium and the distal aspect of the finger. The skin of the right hand was slightly cooler than that of the left, but the pulses were equal and regular. From June 19 to July 1, 1929, hot soaks and codeine gave him some relief, but for the most part the pain in the right upper extremity was becoming more severe. Gradually a line of demarcation at the end of the right index finger formed, involving the nail-bed, eponychium, paronychium and most of the distal anterior closed space. It was difficult for the patient to obtain sleep because of the pain, his appetite was poor, and he was rapidly losing weight.

On July 5, 1929, at 7 a m, he complained of severe headache and pain around the right eye, and asked his brother for a cold application to his head. A few moments later the brother found the patient on the floor, semiconscious and with an apparent paralysis of the left half of the body. A local physician, called immediately, said the patient had a "stroke of apoplexy" and gave a hypodermic injection of morphine. When I saw the patient three hours later he was conscious, recognized people and objects, and presented a typical left hemiplegia. He complained bitterly of frontal and temporal headache on the right side. The local surgical condition presented a more marked line of demarcation, and, strangely enough, palpation of the radial and brachial pulses on the same side failed to elicit any pulsation. The right radial and brachial arteries felt like hard cords under the finger, but the left were normal. The patient was immediately transported by ambulance to the Harkness Pavilion of the Presbyterian Hospital.

Examination here revealed the following. The respirations were quiet and slow (18) and a full pulse was felt on the left side (110), but there were no palpable pulsations in the right upper extremity. The temperature was 99 F. There was asymmetry of the face and left facial paresis. The mouth contained unswallowed, recently eaten food, and the tongue was deviated slightly to the left. The pupils were equal and reacted to light. The lungs were normal, and although the heart sounds were faint they were of normal rhythm and there were no murmurs. The abdomen was heavily muscled and scaphoid, there were no masses or tenderness. The bladder was distended.

There was a flaccid left hemiplegia. The knee, achilles and triceps reflexes were present on both sides but were greater on the left. The right abdominal reflexes were present, the left absent. There was complete sensory loss on the entire left side. The right hand was slightly colder than the left, but the color of the skin was good and the same on both hands.

On July 5, at 12 noon, the blood pressure was 110 systolic and 80 diastolic, at 9 50 p m, the systolic pressure was 140 and the diastolic 95. At this time the radial pulse could be felt. Examination of the blood showed hemoglobin, 70 per cent, red blood cells, 4,500,000, white blood cells, 19,400, polymorphonuclears, 88, lymphocytes, 6, monocytes, 6. The specific gravity of the urine was 1.018, the reaction was alkaline, there was a faint trace of albumin and no sugar. There were few leukocytes and epithelial cells. The Wassermann reaction was negative.

On July 6, during the early morning hours, the patient was conscious but confused. He took fluids and food with difficulty. Hiccup was present. At 9 a m, he was conscious, and the hemiplegia was still present. The right radial and brachial pulsations were absent. The pain in the region of the right temple and eye was increasing.

At 10 a m, Dr. Hubert S. Howe was called in neurologic consultation. Pulsation in the right brachial artery down to antecubital space could be seen and felt. There was occasional pulsation in the right radial artery. A complete neurologic examination was impossible because of the mental condition of the patient. There was a left, flaccid hemiplegia, with involvement of the face, tongue, arm, hand and lower extremity. The abdominal reflexes were absent on the left and active on the right. There was a Babinski sign on the left and a questionable one on the right. There was left hemianesthesia.

At 11 a m, the patient began moving the left extremities, which had remained paralyzed until then.

At 1 p m, he became unconscious and could not be aroused. He was moving all his extremities freely, and the left upper extremity was then so strong and active that a venous puncture could not be done on this side. The respirations

were stertorous and labored. Over the left side of the chest were coarse rolling rales with inspiration. He became paler and slightly cyanotic. The corneal reflexes were absent. The heart sounds were normal. The eyeground was normal in the right eye, and in the left there was a detachment of the retina on the temporal side. The rest of the retinal field was pale. The vessels on the left were smaller than those on the right.

At 4 p. m., the patient was definitely worse. He was still unconscious, and vomitus had to be cleared from his mouth. He suddenly became more cyanotic and ceased breathing, but the pulse continued rapid and palpable for several minutes. Stimulants, intravenous infusion of dextrose and the pulmotor did not prevent death, which was probably caused by asphyxia due to aspiration of vomitus.

During his twenty-nine hours of hospitalization, he voided 1,100 cc. of urine. A postmortem examination could not be obtained.

REVIEW OF LITERATURE

Raynaud himself described cases with cerebral involvement. In one instance, a woman of 62 had transient hemiplegia two years before the onset of symmetrical gangrene. In the third case that he describes, there was paralysis of the right arm. Up to 1916, Momo,³ Osler,⁴ and Norman⁵ made observations in this connection, and the reader is referred to their work for more detailed references in the literature. Since that time there have appeared articles describing many bizarre neurologic manifestations in Raynaud's disease (Weeks and Renner,⁶ Hollis,⁷ Ward,⁸ de Forest,⁹ Sieben¹⁰).

Momo said:

Nearly one-fourth of all patients with Raynaud's disease are reported to suffer or have suffered in the past from phenomena related to disturbances of the nervous system.

Five per cent had convulsions at some time or another and others have had diseases such as congestion of the brain, general paralysis, etc. The patient may be a regular epileptic in whom Raynaud's phenomena began about the same time as or many years after the fits.

3. Monro, Thomas Kirkpatrick. *Raynaud's Disease*, Glasgow, James Maclehose & Sons, 1899.

4. Osler, William. *The Cerebral Complications of Raynaud's Disease*, *Am J M Sc* **112** 522, 1896.

5. Norman, Hubert J. *The Cerebral Associations of Raynaud's Disease*, *Lancet* **2** 1049 (Dec. 23) 1916.

6. Weeks, David F., and Renner, Dan S. *A Case of Symmetrical Gangrene or Raynaud's Disease Associated with Epilepsy*, *J A M A* **66** 651 (Feb. 26) 1916.

7. Hollis, K. E. *Raynaud's Disease of Four Years' Duration. Acute Fatal Termination with Signs of Involvement of Arteries of Central Nervous System*, *Canad M A J* **12**:108, 1922.

8. Ward, E. H. P. *Manic Depressive Insanity and Raynaud's Disease*, *M Rec* **97** 694 (April 24) 1920.

9. de Forest, Henry P. *Raynaud's Disease*, *J M Soc N J* **17** 181 1920.

10. Sieben. *Raynaudische Krankheit und Hysterie*, *Med Klin* **15** 712, 1919.

According to Osler, there are no features of Raynaud's disease suggestive of coarse lesions of the central nervous system. There is a surprising paucity of autopsy reports in the literature to prove clinical interpretations. In one instance, reported by Wigglesworth,¹¹ an insane woman, also epileptic, who had Raynaud's symptom-complex died suddenly after a fit. At autopsy, the pia was slightly thickened, and the brain cord and peripheral nerves were normal to the naked eye. Microscopically, the spinal cord was normal. The peripheral nerves showed 'degeneration of nervous elements and overgrowth of fibrous elements. The epineurium and perineurium were thickened.

SUMMARY AND COMMENT

The patient whose case is reported was a 26 year old Jew, single, born in Austria, who had lived in this country for twenty-three years. He came from a neurotic family. Six years before the onset of his present illness, he suffered from progressive loss of vision in the left eye which was caused by partial detachment of the retina. For three years he had intermittent migrainous attacks on the right side. He had been discouraged by his prospects in life for several years, and could not seem to make any headway, although intelligent and educated. Several months previously he observed a transient coldness and blueness at the tip of his right index finger, eight weeks previously this part of his finger had been bitten by a child. Thereafter he developed progressive dry gangrene of the tip of this finger accompanied by severe pain. On the morning of admission to the hospital, after an attack of severe temporal headache on the right side, he suddenly had a left hemiplegia. For the first time the pulsations of the radial and brachial arteries on the affected extremity could not be felt and the vessels felt like hard cords. In the course of the next twenty-four hours, his pulses could be felt at times. Twenty-eight hours after the inception of his hemiplegia, the paralysis disappeared. He then became unconscious and after progressive cyanosis and stertorous respirations, he suddenly became deeply cyanotic and died in a few minutes—thirty-three hours after the hemiplegia began—probably from asphyxia due to aspiration of vomitus.

Clinically, this patient had Raynaud's disease, with psychic symptoms and several migrainous attacks on the right side over a period of several years. A sudden onset of hemiplegia contralateral to the extremity involved and to the side on which he had temporal headache accompanied by intermittent pulsations of the radial and brachial arteries which could be felt on the affected extremity together with the subsequent

¹¹ Wigglesworth J. Peripheral Neuritis in Raynaud's Disease (Symmetrical Gangrene). *Tr. Path. Soc. London* 38 61, 1887.

disappearance of the paralysis, point to one etiologic factor—transient peripheral and cerebral angiospasm

It is now known that cerebral blood vessels in mammals have vasomotor control (Forbes and Wolff,¹² Kennedy,¹³ Meagher and Ingraham,¹⁴ Talbott, Wolff and Cobb¹⁵) Further, Hiller and Grinker¹⁶ stated "The etiology of many obscure transient nervous syndromes without apparent organic cause may be solved by further study of the possibility of functional circulatory disturbances"

A review of the literature shows that the cerebral symptoms of Raynaud's disease are more frequent than is the usual impression, and that the manifestations may be central, vascular or mental These may precede the obvious clinical syndrome by varying periods of time

12 Forbes, Henry S and Wolff, Harold G Cerebral Circulation III The Vasomotor Control of Cerebral Vessels, Arch Neurol & Psychiat **19** 1057 (June) 1928

13 Kennedy, Foster Epilepsy and the Convulsive State, Arch Neurol & Psychiat **9** 567 (May) 1923

14 Meagher, R H, and Ingraham, F D The Relation of the Cervical Sympathetic Trunk to Cerebral Angiospasm, Arch Neurol & Psychiat **22** 570 (Sept) 1929

15 Talbott, John H Wolff, Harold G, and Cobb, Stanley The Cerebral Circulation VII Changes in Cerebral Capillary Bed Following Cervical Sympathectomy, Arch Neurol & Psychiat **21** 1102 (May) 1929

16 Hiller, Friedrich, and Grinker, Roy R Functional Circulatory Disturbances and Organic Obstruction of the Cerebral Blood Vessels, Arch Neurol & Psychiat **23** 634 (April) 1930

TUBERCULOSIS OF THE STOMACH

AN ANALYSIS OF CASES RECENTLY REVIEWED *

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CINCINNATI

INCIDENCE

From available material it was difficult to determine how frequently tuberculosis of the stomach occurs. Data collected from various sources are given in table 1. There were even fewer data available on which to base an idea of the frequency of the lesion as found at operation on the stomach. At the Mayo Clinic it occurred in 0.035 per cent of the total number of 7,416 gastric operations. Clairmont's¹ report included 2 tuberculous stomachs in 258 gastric operations (0.80 per cent), and Demel's² report included 3 in 1,568 (0.19 per cent). In the data from the Mayo Clinic and the articles just cited, the combined incidence of tuberculosis of the stomach, as discovered at operation, was 0.34 per cent. The average incidence as derived from the total number of necropsies also was 0.34 per cent.

Tuberculosis of the stomach has been known as a disease of the adult male. It has been believed to affect adults and children in the ratio of 3:1. The ratio of male to female has been recorded as high as 5:1 by Melchior, and according to Gossmann and Broders,³ respectively, the ratio is 2.6:1 and 2:1.

PROTECTIVE MECHANISM OF THE STOMACH

Why any segment of the gastro-intestinal tract should be unequally affected by tuberculosis remains as yet unexplained. In theory, biologic factors involved in the protective mechanism of the stomach against the bacillus of tuberculosis include (1) normal gastric juice, (2) intact mucous membrane, (3) paucity of lymph follicles in the gastric wall and (4) normal muscular action.

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*Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery, December 1929.

1 Clairmont, Paul. Bericht über 258 von Prof. von Eiselsberg ausgeführte Magenoperationen, *Arch. f. klin. Chir.* **76**: 180, 1905.

2 Demel, Rudolf. Zur Pylorusstenose auf tuberkulöser Basis, *Deutsche Ztschr. f. Chir.* **183**: 348 (Dec.) 1923.

3 Broders, A. C. Tuberculosis of the Stomach with Report of a Case of Multiple Tuberculous Ulcers, *Surg. Gynec. Obst.* **25**: 490 (Nov.) 1917.

MODES OF INFECTION, LESIONS

Modes of Infection—From an academic standpoint, primary tuberculosis of the stomach has yet to be seen. The cases reported as primary suffer the limitations inherent both in clinical examination and in necropsy. Tuberculous lesions of the stomach are as a rule secondary to some other tuberculous focus in the body, for instance a focus in the lung or in the intestine.

Both experimental and pathologic material leave the question of the mode of infection indeterminate among several possibilities. The blood

TABLE 1—Incidence of Tuberculosis of the Stomach Noted at Necropsy

Author	Total Necropsies	Percentage	Necropsies in Tuberculous Subjects		Tuberculous Stomachs
			Subjects	Percentage	
Clayton and Wilkinson quoted by Sappington Bahnenmonat Month 55 227 1920	7 169	0 70			70
Eisenhardt quoted by Bretzner Berl klin Wchnschr 57 1237 1920			6 000	0 016	1
Glaubitt, quoted by Zesas Centralbl f d Grenzgeb d Med u Chir 16 448 1913	12 528	0 37	2,237	2 10	47
Gossmann Witt u d Grenzgeb d Med u Chir 26 771 1913	5 900	0 30	2 360	0 80	18
Grusdew quoted by Zesas Centralbl f d Grenzgeb d Med u Chir 16 448 1913	18,593	0 12			23
Heubschmann Antomie der Tuberkulose Berlin 8 p 300	10,000	0 10			10
Kundrat quoted f d Grenzgeb d Med u Chir 11			418	0 48	2
Letulle quoted by Zesas Centralbl f d Grenzgeb d Med u Chir 16 448, 1913			180	0 55	1
Melchior L Beitr z Klin d Tuberk 26 2 1913		0 70	848		6
Ophuls A Statistical Survey of Three Thousand Autopsies Stanford University Stanford University Press 1926 vol 1, p 144	3 000	0 00	632	0 00	0
Orsos Deutsche Ztschr f Chir 191 306 (June) 1925	6,280	0 08			5
Plambeck quoted by Biernath Deutsche med Wchnschr 47 1091, 1921			490	0 60	3
Robertson H E Personal communication to the author	8,401	0 00		0 00	0
Simmonds Munchen med Wchnschr 47 317 1900			2,000	0 40	8

stream as a route is more generally favored than the lymph stream. Infection by ingestion or spread by continuity or contiguity with adjacent tuberculous organs at times can be demonstrated.

Lesions—Excluding in tuberculous subjects diffuse, generalized, nonspecific inflammations, mucosal erosions and generalized milary tuberculosis of the stomach, there remain to interest the surgeon the more focal tuberculous lesions associated with ulcer, tumor, scarring and their combinations.

The tuberculous ulcer predominates, it can be single or multiple, varying in diameter from a few millimeters to as much as 10 cm. In its typical although infrequent form, the ulcer presents undermined ragged edges and a dirty, grayish-yellow base covered at times with

visible tubercles. It usually does not extend more deeply than to the muscle layer. Perforation seemingly is its least characteristic feature. Hemorrhage from the ulcer is not so uncommon. The situation of the ulcer usually is along the lesser curvature in the pyloric end of the stomach, with a tendency toward appearing on the posterior wall.

The chief characteristic of the tumor is its mass, often associated with an ulcer. At times there is early caseation and liquefaction under the intact mucous membrane and production of an abscess of the gastric wall. The abscess may rupture in sieve-like fashion into the lumen of the stomach to form multiple ulcers, or interstitial cavernous gastritis. Cirrhosis and cicatrization are the earmarks of the scar form. This and the tumor form also are found most often in the pylorus.

With a tuberculous lesion of the stomach there is commonly early involvement of regional lymph nodes and a tendency to early caseation. In practice, perhaps because of unfamiliarity, there is little concern for the gross appearance of a gastric lesion that would mark it as tuberculous unless tubercles were visible. The nature of the lesion is established only by microscopic examination. The microscopic tubercles are most numerous about the muscularis mucosae. Demonstrating the organisms with proper stains is tedious and difficult.

ASSOCIATION OF GASTRIC ULCER, CARCINOMA AND TUBERCULOSIS

Tuberculosis of the stomach mimics and is always confused with the signs and symptoms of gastric ulcer, carcinoma or their complications.

The coincidence of gastric carcinoma and gastric tuberculosis was observed by Faltin⁴ only twelve times. In a man 62 years of age, with tuberculosis of the apex of the right lung, he found adenocarcinoma in a tuberculous ulcer. Anschutz and Konjetzny⁵ found a single tubercle in the margin of a gastric carcinoma, and in the regional lymph nodes there were both carcinomatous metastasis and caseous tubercles.

An organic gastric lesion, associated with pulmonary tuberculosis, is almost bound to be a gastric ulcer or a carcinoma, therefore, the patient, unless he is in the terminal stage of tuberculosis, should be accorded abdominal exploration. During the period in which the two reported cases occurred at operation at the clinic, 2,963 operations were performed on the stomach for carcinoma and 1,952 operations on the stomach for ulcer.

⁴ Faltin R. Simultaneous Occurrence of Tuberculosis and Cancer in the Stomach. *Finska Lak-sällsk handl.* 68:659 (July) 1926, Gleichzeitiges Vorkommen von Tuberkulose und Carcinom im Magen. *Acta chir. Scandinav.* 61:331, 1927.

⁵ Anschutz Willy and Konietzny, G. E. Kombination des Magenkarzinoms mit Magentuberkulose in. *Die Geschwulste des Magens*, Deutsche Chir. Stuttgart Stuttgart Ferdinand Enke 1921 46 f. pp. 240-242.

DIAGNOSIS, PROGNOSIS AND TREATMENT

Diagnosis—The accurate clinical diagnosis of tuberculosis of the stomach is difficult, if not impossible. There is nothing distinguishing about either the history or the observations on general examination to indicate the tuberculous nature of a gastric lesion. An associated active pulmonary lesion can only arouse suspicion. Tuberculosis of the stomach is met with at operation just as frequently in subjects in whom no other tuberculous focus can be demonstrated. Of the organic defects of the stomach, as revealed by the roentgen ray, none is sufficiently characteristic to furnish a diagnosis of tuberculosis of the stomach. With present methods, the disease will continue to be confounded with gastric ulcer and with carcinoma.

Prognosis and Treatment—The comfort derived from surgical measures for a tuberculous gastric lesion justifies the risk entailed. When the gastric lesion is the only manifestation of tuberculosis, removal should lead to cure. Tuberculosis of the stomach eventually needs surgical treatment. There seems to be but a feeble tendency to early or complete healing, and in some cases, a rapid tendency to pyloric obstruction. A gastric lesion and its complications in the trials of a patient with pulmonary tuberculosis affect one of the deciding issues, the state of nutrition. If the state of nutrition is maintained, it may make it otherwise possible to arrest or heal the pulmonary lesion under medical treatment. Whatever the surgical procedure may be, it must fit the physical state of the patient. Jejunostomy, gastro-enterostomy and gastric resection have their indications.

MATERIAL

In 1917, Broders published a report of a case of tuberculosis of the stomach in a patient who underwent surgical treatment. He included an analysis of the cases reported until then, and classified them as positive, probable, doubtful and rejected. Since Broder's report, thirty-three additional reports of cases have been reviewed from the literature and two other cases have been seen at the Mayo Clinic. According to the classification which Broders employed in his paper, two of the thirty-five cases which form the basis of my study would qualify as positive cases and twenty-four as probable cases of tuberculosis of the stomach. The remaining nine cases were excluded because they fell into the doubtful or rejected groups or because surgical treatment was not employed. If a histologic picture of tuberculosis is to be acceptable at all, those cases classified as probable on the basis of a microscopic picture of tuberculosis were cases of tuberculosis of the stomach.

The twenty-six cases (table 2) which remained after nine of the thirty-five had been excluded were subjected to analysis in the hope

that through recent refinement in both clinical and laboratory methods of examination some criteria could be found which would aid in clinical recognition of the gastric lesion

The sexes were about evenly represented, in the twenty-five cases in which sex was noted, thirteen were males and twelve were females

TABLE 2—*Source of Case Reports*

	Probable Cases
Albu in <i>Spezielle Pathologie und Therapie innerer Krankheiten</i> , Berlin Urban & Schwarzenberg 1921, vol 5 p 993	1
Baetzner <i>Berl klin Wchnschr</i> 57 1237 1920	1
Bertolini <i>Osp maggiore</i> 9 197 1921	2
Biernath <i>Deutsche med Wchnschr</i> 47 1091 1921	1
Demel	2
Faltin	1
Friedman G A J A M A 72 101 (Jan 11) 1919	1
Hartmann and Renaud <i>Bull et mem Soc anat de Paris</i> 90 357 1920	1
Hofer <i>Beitr z klin Chir</i> 126 555 1922	1
Hurst <i>Guy's Hosp Rep</i> 75 428 (Oct) 1925	1
Mayo Clinic	2
Meisner E <i>Mitt u d Grenzgeb d Med u Chir</i> 39 205 1926	5
Orsos	1
Razzaboni <i>Policlinico (sez chir)</i> 26 153 1919	1
Rother <i>Berl klin Wchnschr</i> 55 1049 (Nov) 1918	1
Severin <i>Berl klin Wchnschr</i> 54 738 1917, <i>Deutsche med Wchnschr</i> 52 1168 1926	1
Spengler <i>Med klin</i> 17 101 (Jan 23) 1921	1
Suermondt <i>Nederl Tijdschr v geneesk</i> 1 2309 1925, abstr J A M A 85 236 (July 18) 1925	1
Willerding <i>Arch f klin Chir</i> 128 109 1924	1
Total	26

TABLE 3—*Symptoms and Signs of Tuberculosis of the Stomach*

Symptoms and Signs	Present Cases	Absent Cases	Not Recorded
Pain after food	24		2
Loss of weight and strength	23		3
Vomiting	19	3	4
Free hydrochloric acid	15	7	4
Tuberculosis elsewhere	12	12	2
Palpable tumor	9 (3%)	11	3
Hemorrhage			
From mouth	3 }		
From bowel	5 }	5	10
Constipation	8	3	15
Diarrhea	4	5	17

The ages ranged from 18 to 62 years, and averaged about 38½ years. The third decade of life was represented by the greatest number.

The gastric symptoms and signs (table 3) were present for periods varying from three weeks to sixteen years and averaged close to two years. The most constant symptoms were epigastric pain after meals, loss of weight and strength and vomiting. Epigastric pain after eating was present in twenty-four cases. In twenty-three cases in which loss of weight and strength were mentioned, they were recorded as being present. In twenty-two cases vomiting was recorded as present in nineteen (86 per cent) and as absent in three. In the total of twenty-

six cases, hemorrhage from the mouth was recorded three times, and from the bowel, five times. Constipation and diarrhea, judging from the number of times that they were not mentioned, seemingly were of little significance, but constipation was mentioned a few more times than diarrhea. In twenty-two cases, free hydrochloric acid was recorded as present in fifteen (68 per cent) and as absent in seven. In the series it ranged from 0 to 65, and averaged about 16.

The preoperative diagnosis included gastric ulcer in eight cases, gastric carcinoma in four and pyloric obstruction in six. Tuberculosis of the stomach was thought of but once. In six of the cases in which the diagnosis was combined ulcer and pyloric obstruction, the presence of a malignant lesion could not be ruled out.

Nine (39.1 per cent) of twenty-three cases presented definite tumors on palpation in the upper part of the abdomen, three (13.1 per cent) had questionably palpable tumors and eleven (47.8 per cent) did not present a mass.

In twelve of twenty-four cases, there were manifestations of tuberculosis elsewhere in the body. In cases in which tuberculosis was present elsewhere, pulmonary lesions were represented in 100 per cent. Besides pulmonary involvement, in one case there were lesions of bone and in another, tuberculous epididymitis.

In twenty (77 per cent) of twenty-six cases, roentgenologic examination revealed some sign of organic gastric defect. Hour-glass deformity was represented in two cases.

Radical surgical treatment predominated. In twenty cases (77 per cent) some type of gastric resection was done. The Billroth II type of anastomosis was done in ten cases and the Polya type in two, excision of the lesion, combined with gastro-enterostomy, was done in two, a Kocher gastroduodenostomy was done in one case and the type of resection was not recorded in five cases. Gastro-enterostomy alone was done in five cases and biopsy alone in one case.

Concerning the possibility of recognizing the lesion at the time of operation, tuberculosis was mentioned in only one case, a case in which tubercles were visible. The nature of the lesion was surmised in three cases, in two cases the lesion was called carcinoma and in two it was questioned as being carcinoma.

Of the twenty-four cases in which the result is known, nineteen (79 per cent) patients survived the operation and five (21 per cent) died. Two patients were alive and well, respectively, three and a half and ten years after operation. Both were operated on for carcinoma of the stomach, in neither case was there clinical evidence of tuberculosis elsewhere in the body. There were two deaths, respectively, in one month and in two and a half years after operation, both from tuberculosis.

The tuberculous gastric lesions in the twenty-six cases were as follows: ulcer only, ten cases; tumor and ulcer, ten; tumor only, three; miliary only, two; and miliary with tumor, one case.

The parts of the stomach involved included the pylorus in seventeen cases, the lesser curvature in nine cases, the posterior wall in seven cases, the anterior wall in four cases and the greater curvature in two cases.

REPORT OF CASES

CASE 1.—A man aged 40 presented himself at the Mayo Clinic on Feb. 1, 1927, complaining of pain in the stomach and of abdominal distention. He had been married for seven years, his wife and two children enjoyed good health. For the five years before he came to the clinic he had had a periodic, continuous, gnawing epigastric pain aggravated by the taking of food, and lasting from one to two weeks, with respites of from two to three months. When the pain had been present the epigastrium had been sore to the touch. After two years, the pain had increased in severity and the attacks had increased in duration sufficiently to become inconvenient and to cause marked failure of the appetite. He had borne the severer spells for another year and then had sought medical aid. On investigation elsewhere, a gastric ulcer had been diagnosed clinically and had been confirmed roentgenologically. Tonsillectomy and a medical regimen had been carried out with immediate but temporary relief. The pain and disability had returned to such a degree that the patient had been confined to bed for intervals of from one to two days. At the time he arrived at the clinic there was no relief from taking food, but some relief from taking sodium bicarbonate. Complete relief was always obtained by inducing vomiting. There was no pain at night. Until one year before he came to the clinic his weight had been stationary but since then he had lost as much as 40 pounds (18.1 Kg.).

General examination revealed a fairly healthy, undernourished-looking man 5 feet 9¾ inches (176.13 cm.) tall, weighing 106 pounds (48.1 Kg.). The temperature was normal. The heart and lungs appeared to be normal. Abdominal examination disclosed only a palpable, slightly tender mass in the region of the pylorus. The urine was normal to examination, the concentration of hemoglobin was 76 per cent, leukocytes numbered 5,300 in each cubic millimeter of blood. Analysis of the gastric content disclosed total acidity equivalent of 56 (56 cc. of tenth-normal sodium hydroxide neutralized 10 cc. of filtered gastric content). The free hydrochloric acid was estimated as 40. The quantity of gastric content recovered was 120 cc. The Wassermann reaction of the blood was negative. Roentgenologic study of the thorax gave negative results on two occasions. The gallbladder appeared to be normal on roentgenologic examination, but the gastric roentgenoscopic examination revealed a small ulcer, interpreted as benign, situated on the lesser curvature at the angle of the stomach.

Exploration of the ulcer was advised and was done on February 10. Along with an ulcer at the middle of the lesser curvature of the stomach was a large, infiltrating, indurated area in the gastric wall associated with a large number of hard, enlarged lymph nodes in the lesser omentum. Several of the latter were removed for examination. Partial gastrectomy with a Billroth II type of anastomosis was done.

In the resected portion of the stomach there was an apparently inflammatory lesion and a superficial ulcer without a crater. The lymph nodes also, to all appearances, were inflammatory. Microscopically, both the gastric lesion and the

lymph nodes presented the picture of tuberculosis. The mucous membrane generally was intact, but it displayed a rich, lymphocytic cellular reaction, with scattered foreign body giant cells, with and without the formation of tubercles. The lymph follicles were not involved. The submucosa was thick and compact and gave evidence of hyaline changes. It also contained tubercles of typical structure within its upper half, toward the muscularis mucosae. There were many congested blood vessels surrounded by lymphocytic infiltration. The muscle layer was swollen and hyalinized, and there was some increase of connective tissue and cellular reaction. The predominating reacting cells were lymphocytes, but near the serosa there were regions of polymorphonuclear cells. The organisms were sought for but were not found.



Fig 1 (case 1)—Typical tubercle formation at the muscularis mucosae, $\times 75$

The postoperative convalescence was uneventful. Examination, on October 31, revealed that the only complaint was of gas and discomfort in the abdomen associated with overeating and the ingestion of milk. The weight was 112¼ pounds (51.1 Kg). The urine again was normal, the concentration of hemoglobin was 74 per cent. Many blood cell counts were within normal limits. Analysis of the gastric content disclosed achlorhydria, and a total acidity of 22, bile was present in abundance. Again the thorax did not present clinical signs of tuberculosis. Roentgenograms of the colon gave evidence of normal conditions, those of the stomach indicated that the lumen at the point of gastro-enterostomy was free.

The patient was well in July, 1929, but was somewhat underweight and nervous.

CASE 2—A man, aged 56, presented himself at the clinic on June 28, 1923, complaining of his stomach. One of his sisters had died of tuberculosis at the age of 40. His wife and daughter were in good health. At the age of 9 years he had had scrofula which had manifested itself in the spinal column and right

groom At the ages of 27 and 42, he had had sieges of illness called typhoid fever Between the ages of 40 and 46 he had begun to have periodic attacks of epigastric pain coming on late after meals, these attacks occurred for six weeks at a time in warm weather At the age of 44, in the course of one of his attacks, he was seized with an agonizing epigastric pain Operation was performed immediately Afterward he was told that he had had a perforating gastric ulcer, which had been closed His previous disability soon returned and was complicated by vomiting Five years later, during an attack, he experienced great weakness and loss of weight, at one time, a hemorrhage from the stomach had resulted in loss of a quantity of blood estimated to be at least a liter He had submitted to a medical regimen, and his condition had begun to improve at once He had vague recollections of having had slight epigastric discomfort since then, during the summer There had been no pain at night, overwork and riding in the saddle had caused the distress to return From October to December, 1927, he had felt well for the first time in years Then he had begun to note in the mornings, a sensation as if a ball were rolling around in his stomach Riding in the saddle had begun to nauseate him and he had begun to lose appetite and also weight Bloating, belching and vomiting, of food eaten as long as twelve hours before, had set in On one occasion there again had been blood-tinged vomitus, in two months the patient had lost 15 pounds (6.8 Kg)

General examination revealed an emaciated dehydrated man, 5 feet $5\frac{1}{2}$ inches (166.37 cm) tall, weighing 127 pounds (57.6 Kg) There was marked dorsal scoliosis and kyphosis, with small, crusted, superficial ulcers over the bony prominences of the back Examinations of the heart and lungs did not give significant results, except for the marked thoracic deformity The abdominal organs apparently were normal There were scars marking the site of the scrofula in the groin and an incisional scar on the abdomen Analysis of gastric content disclosed a total acidity of 50 and free hydrochloric acid of 34 Blood was present in the aspirated content The Wassermann reaction of the blood was negative Urinalysis, except for an occasional pus cell, disclosed normal conditions The concentration of hemoglobin was 74 per cent, the leukocytes numbered 4,200 in each cubic millimeter of blood Roentgenologic examination of the thorax gave evidence of old pleuritic adhesions to the right side of the diaphragm, old destructive arthritis of the tenth and eleventh thoracic vertebrae, with fusion, and marked angulation of the spinal column The interpretation of the gastric study was that there was an ulcer, probably malignant, on the posterior wall of the stomach at the angle A preoperative diagnosis of probable carcinoma superimposed on a gastric ulcer was made, and exploration of the lesion was advised

The patient was hospitalized for the purpose of feeding him and building up his ability to take fluid Operation was done on July 3, 1928 Well around on the anterior aspect of the stomach was a fine, white line that was taken to be the mark of previous closure of a perforation Above this line, and extending posteriorly, an ulcer, with a crater 2 cm in diameter, was palpable Even though the stomach was adherent posteriorly, the only advisable procedure seemed to be resection of the stomach About half of the organ was removed, and a posterior type of Polya anastomosis was made The resected specimen presented marked thickening, induration and unevenness of the gastric wall, together with an ulcerated area 2 cm in diameter, with no distinguishing marks

Microscopic examination of the gastric wall and of the lymph nodes, attached in the omental tags disclosed a tuberculous process All the layers of the stomach were greatly thickened The mucosa, where it was intact, seemed swollen and richly invaded by lymphocytes The lymph follicles were large, the germinal

centers were thin and the denser peripheral zones were irregularly drawn out, far toward the surface of the mucous membrane, the follicles were free from involvement by tubercles. Beneath the muscularis mucosae, tubercles with and without giant cells appeared as large clear whorls, with a very slight lymphocytic reaction about them. The submucosa was greatly thickened by an increase in the hyalinized fibrous tissue. The blood vessels were large, fairly numerous and distended. There was an occasional small, free hemorrhage. In the entire layer, there was an absence of cellular reaction. The hyaline-like muscle layer presented swollen bundles of muscle fibers widely separated as much by edema as by an increase of connective tissue. The serosa was approximately twice as thick as the layer of muscle, it was edematous, and was rich in hyalinized fibrous tissue. The blood vessels were congested and one vessel was thrombosed. There were no tuberculous formations near it. Along the edge of the ulcer, where the mucous membrane

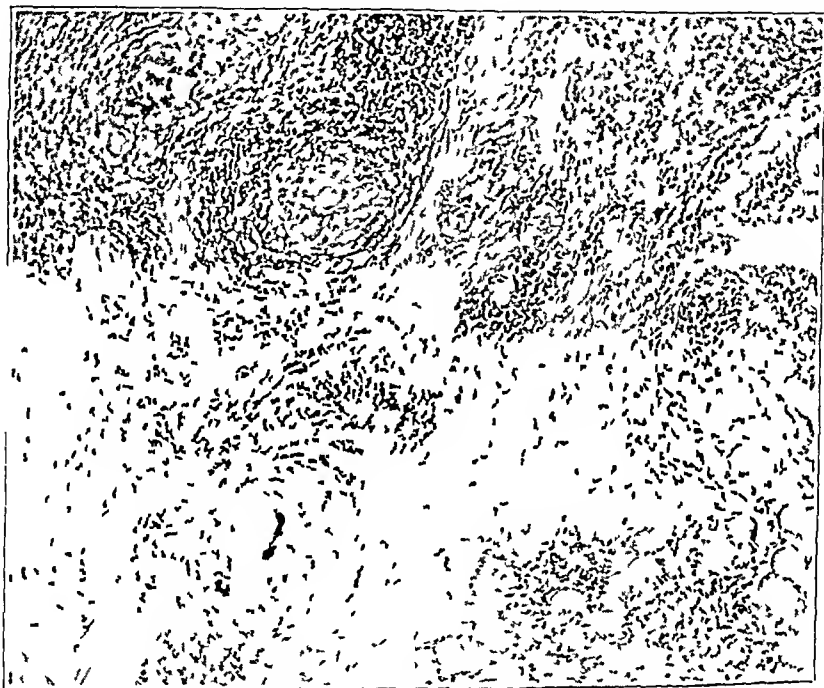


Fig 2 (case 2) —Tubercle formation along the muscularis mucosae, $\times 75$

was still recognizable but not intact, typical tubercles, with rich polymorphonuclear exudate, were present. The necrotic center of the ulcer went through to the layer of muscle. For a wide margin about the necrotic area there was an extremely dense eosinophilic cellular reaction, which at points where the ulcer and muscle came in contact extended throughout the layer of muscle. The necrosis in the bed of the ulcer did not appear to be caseation necrosis. Nothing resembling tubercles was noted in its vicinity. The regional lymph nodes were all but replaced by noncaseating tubercles, the germinal follicles were uninvolved. Organisms were sought for, but were not found.

The patient died on the seventh postoperative day, from circulatory collapse complicated by diffuse pneumonia.

At necropsy, the major anatomic diagnoses were bilateral, massive coalescing bronchopneumonia, healed lesions of adhesive pericarditis and pleuropericarditis, healed lesions of tuberculosis of the lungs and spinal column and arteriosclerosis. What seemed to be about a third of the stomach remained and appeared normal.

Microscopic examination of specimens from the lower lobe of the left lung, the spleen, an aortic lymph node and the lesser omentum disclosed more or less typical formation of tubercles

Comment—Case 1 is typical of those reported as examples of primary tuberculosis of the stomach. It is the type that lends itself favorably to a good prognosis.

Case 2 presents much evidence of previous tuberculosis elsewhere in the body, arrested, if not healed. There is no evidence on which to base a belief that the long history of gastric disturbance, marked by an acutely perforating ulcer, was caused by tuberculosis of the stomach from the beginning.

The history in each case was fundamentally that of gastric ulcer. There was no difficulty by clinical and laboratory means in establishing the presence of a gastric lesion.

SUMMARY AND CONCLUSIONS

Tuberculosis of the stomach is a rare disease of adults. The outstanding elements accompanying the chronic dyspepsia are pain after meals, loss of weight and strength and vomiting. Half of the cases are associated with tuberculosis elsewhere in the body. The disease is mistaken for gastric ulcer or carcinoma. Symptoms of pyloric stenosis are common. The treatment is surgical, and by choice consists of radical resection of the lesion-bearing portion of the stomach. The pyloric end of the stomach is the site of predilection. In most instances, the gross appearance of the lesion, except for the presence of an ulcer, a tumor, scarring or combinations of the three lesions, does not identify itself as tuberculous unless visible tubercles are present. The real nature of the lesion is revealed only by microscopic examination. Bacilli of tuberculosis are difficult to demonstrate in the lesion.

The presence of an organic gastric lesion can be relatively easily established. If surgical treatment is prescribed for all chronic organic gastric lesions, the rare disease of tuberculosis of the stomach does not create a new problem.

In most instances evidence of tuberculosis elsewhere in the body is not a contraindication to exploration of a gastric lesion.

Tuberculosis of the stomach is diagnosed by histopathologic methods. There is no need clinically to differentiate tuberculosis of the stomach from the commoner chronic organic gastric lesions in order to institute the proper treatment.

THE RÔLE OF THE PYLORIC SPHINCTER IN THE BEHAVIOR OF GASTRIC ACIDITY

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It is the purpose of this report to present observations on certain changes in the behavior of gastric acidity which follow experimental diminution in the activity of the pyloric sphincter (pyloric insufficiency). In previous communications¹ from this laboratory experiments were described which indicated that reflux of alkaline pancreatic juice into the stomach was probably an important factor in the regulation of the level of gastric acidity. One might expect as a corollary that the pyloric sphincter governs this regurgitation in a decisive way. Direct roentgenologic observations of such a phenomenon have been made in human beings by Salamond². The present experiments add further support to the theory.

PREVIOUS WORK

That there is a relationship between gastric acidity and the pyloric muscle has long been noted from a great variety of evidence³ which need not be reviewed here. A succinct statement of this relationship was advanced in 1907 by Cannon⁴ in a theory called the "acid control of the pylorus," which stated that acid, on the stomach side opened, and on the duodenal side closed, the pylorus. On that basis, the gradual emptying of the stomach was explained.

For a great many years this theory was quite generally accepted, and undoubtedly accounts for a good many facts. The theory fails, however, to explain a number of phenomena, many of which Cannon himself called attention to in his original communication. One of the significant objections is that it does not explain how the pylorus opens

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1 Elman, Robert. Probable Influence of Pancreatic Juice in the Regulation of Gastric Acidity, *Arch Surg* **16** 1256 (June) 1928, *Surg Gynec Obst* **49** 34 (1929). Olch, I. Y. Duodenal Regurgitation as a Factor in Neutralization of Gastric Acidity, *Arch Surg* **16** 125 (Jan) 1928.

2 Salamond, R. W. A. *J Radiol* **11** 453, 1928.

3 Rabkin, B. P. *Aeusserer Sekretion der Verdauungsdrüsen*, ed 2. Berlin: Julius Springer, 1928. p. 801.

4 Cannon, W. B. *Am J Physiol* **20** 283, 1907.

in patients with anacidity, a condition which we now know is not infrequent in healthy persons. Indeed, in such persons in spite of the absence of acid there is often fluoroscopic evidence of a patulous pylorus and an increased emptying time. Hyperacidity, on the other hand, with or without symptoms, instead of accelerating pyloric opening, is frequently associated with pylorospasm and delayed emptying. It has been repeatedly shown, moreover, in experiments on both laboratory animals and man,⁵ that within normal limits the more acid the test solution the more slowly it leaves the stomach. Cannon explained the latter facts by stating that the stronger acid, requiring longer for its neutralization on reaching the duodenum, thus maintains closure of the pylorus and delays emptying. This conception emphasizes the importance and necessity of neutralization of acid but does not support the part of the theory concerned with the rôle of acid on the stomach side in opening the pylorus. The neutralization of acid undoubtedly plays a most decisive rôle, but, as indicated by the evidence already referred to,¹ it probably occurs in the stomach through reflux of pancreatic juice rather than in the duodenum directly.

One of the great difficulties in explaining the evident relationship which nevertheless exists between the pyloric sphincter and gastric acidity is the problem of measuring the degree of activity of the pylorus, which has been called by Carman⁶ the great "X quantity" in roentgenologic investigation of the stomach. Most observers have taken the emptying time of the stomach as a measure of pyloric activity even though factors other than the opening and closing of the "tonus" of the sphincter may be of even greater significance. Certain of them, it is true, may be standardized such as the kind of food, or its bulk or fluidity. Neuromuscular factors, however, such as gastric peristalsis and "gastric tone" as well as the important influence of the amount of food in the duodenum,⁷ are usually beyond control. A still further source of confusion has been the use of various "test meals" to evoke a gastric response or, more particularly, acidity in the contents of the stomach. The results are generally of great variability even when produced by simple means. When excited by protein the degree of acidity developed is frequently masked by its combination with the test substance. In any case the acidity measured does not really represent the true gastric response, but, as pointed out in our previous papers, is probably a resul-

5 Serdjukow, A. S. Diss., St. Petersburg, 1899, cited by Babkin (footnote 3, p. 802). Hedblom, C. A., and Cannon, W. B. *Am. J. M. Sc.* **108**: 504, 1909. Moritz. *Ztschr. f. Biol.* **42**: 589, 1901.

6 Carman, R. D. *Roentgen Diagnosis of Diseases of Alimentary Tract*, ed. 2, Philadelphia, W. B. Saunders Company, 1921, p. 1929.

7 Alvarez, W. C. *The Mechanics of the Digestive Tract*, ed. 2, New York, Paul Hoeber, Inc., 1928, p. 178.

tant of two factors, gastric secretion and neutralization, the latter factor being frequently overlooked. Variations are therefore not surprising and make deductions all the more difficult. An interesting review of the entire question of the control of the pylorus can be found in the recent monograph by Alvarez.⁷

Experiments directed toward altering the pylorus itself with subsequent study of gastric acidity have been few. In general, gastric acidity has been found much lower both in human beings and in dogs following various types of pylorotomy.⁸ Thompson⁹ has recently shown experimentally that this change is greater the more completely the pylorus is removed. He also proved that this reduction is not due to alterations of secretion, for the juice from a Pavlov pouch in such dogs showed a normal acidity. After pyloroplasty in which the sphincter is cut across a similar lowering of gastric acidity has been observed both in human beings¹⁰ and in dogs.¹¹ Deaver and Burden¹² have recently removed the anterior half of the entire pyloric wall in man for pylorospasm and duodenal ulcer. Reduction of gastric acidity was not observed, although the patients were reported as greatly relieved by the operation. Unfortunately, in all these operative procedures structures other than the sphincter are altered, so that clear inferences are unjustified. The simplest form of pyloric insufficiency, such as may be produced by cutting across the muscle alone, has apparently escaped experimental study, at least from the point of view of its effect on gastric acidity. Strauss¹³ removed a triangular piece of the pyloric muscle in dogs and noted a persistent lowering of the emptying time, but reported no observations on gastric acidity. Incision of the hypertrophic pylorus in infants is a frequent operation, but no studies of the contents of the stomach have apparently ever been made in them. It is interesting however, that a few years ago Zahorsky¹⁴ described a condition (he called it the "Zed reaction") which immediately followed the Rammstedt operation for the relief of pyloric stenosis in infants. The prominent symptom was watery diarrhea in spite of a gain in weight. That this was probably due to the sudden development of intestinal regurgitation is shown by the finding of *Bacillus coli* in the stomach in such cases. That an anacidity also exists is made likely by the fact that clinical cure results from the feeding of acid to these infants. Indeed,

8 Babkin (footnote 3, p. 443)

9 Thompson, H. L. Proc. Staff Meet., Mayo Clin. 5: 88, 1930

10 Finney, G. G. Personal communication to the authors

11 Olch (footnote 1, third reference)

12 Deaver, J. B., and Burden, V. G. S. Clin. North America 9: 1003, 1929

13 Strauss, A. A. Longitudinal Resection of the Lesser Curvature, J. A. M. A. 82: 1765 (May 31) 1924

14 Zahorsky, J. M. Clin. North America 9: 117, 1926

the use of lactic acid milk is said to have received much impetus from its success in such cases ¹⁵

METHODS

The behavior of gastric acidity was studied in a special way by means of an "acid test meal." Healthy dogs of from 8 to 12 Kg. were selected, and after an appropriate fast were given 200 cc. of 0.5 per cent hydrochloric acid by gavage, samples were removed every twenty minutes and titrated for "free" and "total" acid. A "neutralization" curve was then plotted which represented, not the gastric response to a stimulus, but the effectiveness and rapidity with which acid, once present in the stomach, is neutralized and discharged into the duodenum. A detailed description of this method and a discussion of its advantages will be found in our previous papers ¹⁶. Normal curves varied but little between dogs of the same size. Nevertheless, two or three tests were often made preparatory to operation.

Operations were carried out with aseptic precautions and under complete ether narcosis. Through a right rectus incision the pylorus was brought up into the wound. With careful use of a sharp scalpel all the circular pyloric fibers were cut by a longitudinal incision across them carried down to the submucosa. It was necessary to be sure that all fibers were severed else regeneration rapidly took place. Perforation, on the other hand, had to be avoided in order to obviate the scarring and narrowing which followed suturing it. A good pout or bulge of the submucosa into the incision attested the completeness of the dissection. Any slight bleeding was usually controlled readily by a hot pack. Only occasionally was a ligature necessary. The raw area was then carefully covered with omentum which prevented the growth of scar between the cut ends of the muscle and precluded the development of adhesions to surrounding structures. The wound was then closed in layers. Observations on the neutralization of the "acid test meal" were carried out within fourteen days after operation and for varying periods up to ten months. The animals were killed with chloroform and the condition of the pylorus carefully noted. Control experiments consisted of similar incisions over the duodenum and prepyloric antrum and of simple laparotomy.

OBSERVATIONS

In a great many control dogs there was no change in the neutralization curve even after two or more operations, other than cutting of the pylorus, were performed in the same animal. In several early experiments no change or only a transient one was noted even after division of the pyloric sphincter or excision of part of it. In each of these cases it was found at autopsy that pyloric insufficiency had not been achieved. The incision was incomplete, new muscle or fibrous tissue had grown across the incision, or there were firm adhesions between the pyloric scar and liver or the gallbladder. But in eight dogs permanent changes were observed which were considered satisfactory for the experiment. Four died of accidental causes at periods shorter than four months after operation. Four of them lived from four to ten months,

¹⁵ Hartmann, A. F. Personal communication to the authors.

¹⁶ Elman (footnote 1, first and second references).

after which observations were discontinued. These experiments will be described in detail. In each case at autopsy a complete pyloric insufficiency was demonstrable by the pouting or bulging of the submucosa through the incision and the absence of adhesions between it and the surrounding organs. (See figs 2, 3 6 and 8)

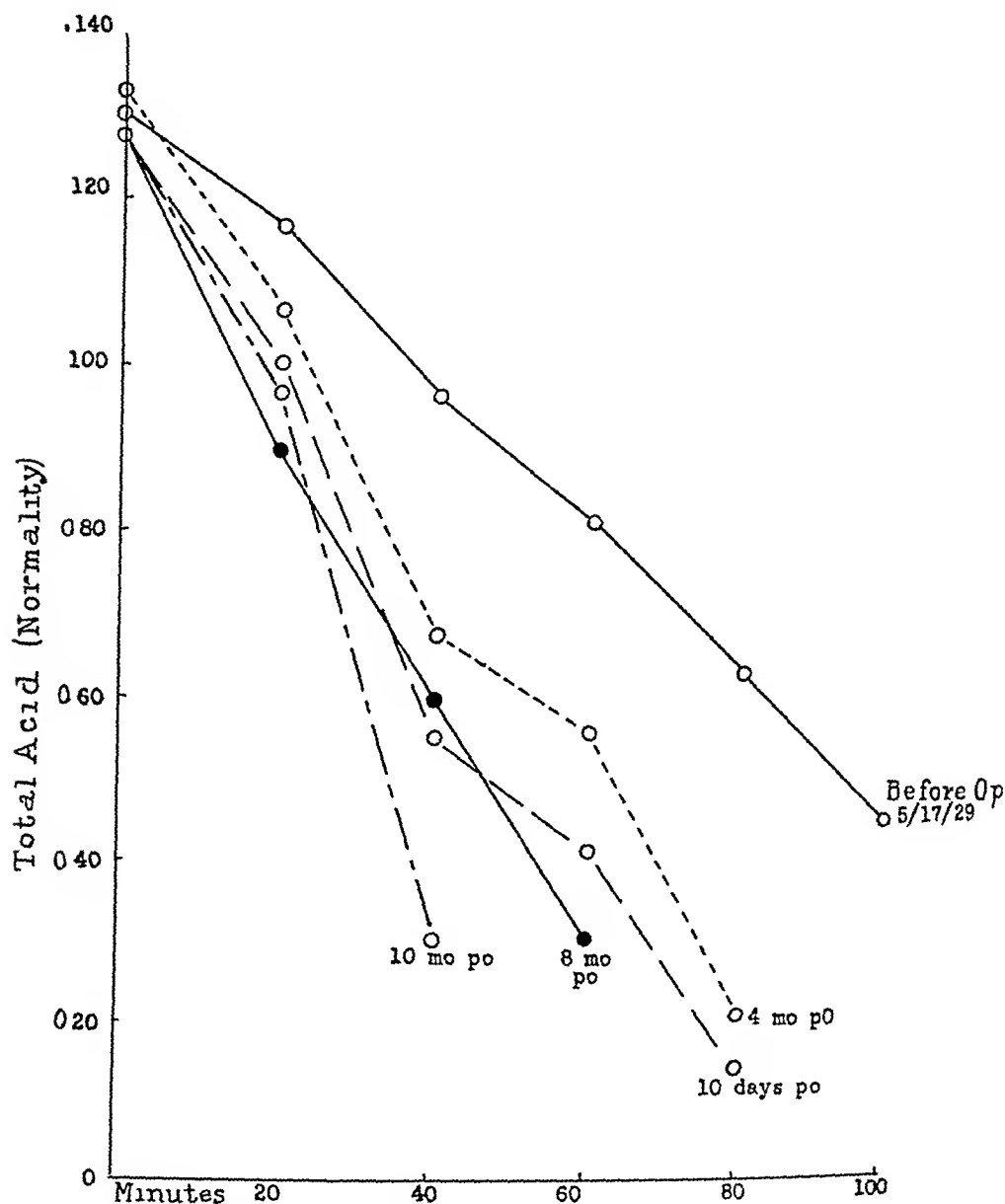


Fig 1—Neutralization curves for dog 349, weighing 12 Kg. The dog was killed on March 25, 1930, and showed a definite pouting at the pylorus with no adhesions. Figure 2 represents the gross specimen and figure 3 a section through the pylorus.

The change was apparent soon after operation (the earliest observations were made on the fifth day) and consisted in a more rapid drop in the acidity of the test solution and usually a quicker emptying time.

The observations are represented in the accompanying charts (figs 1, 4, 5 and 7), which are self-explanatory. The control experiments were negative and will not be mentioned further, since one is represented in dog 161, in which such control observations were made previous to the



Fig 2—Photograph of gross specimen from dog 349. The lumen of the specimen was filled with water before fixation. The arrows show the pouting of the submucosa through the pyloric incision.

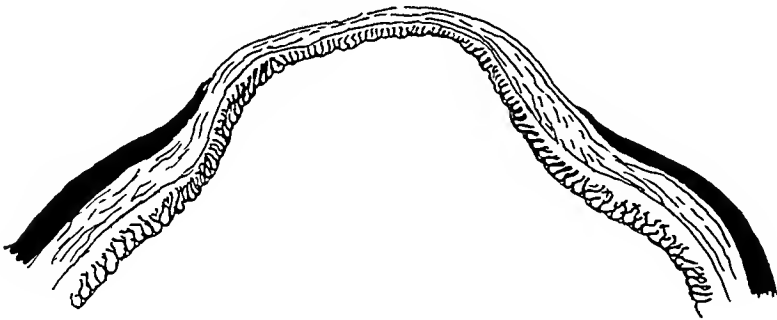


Fig 3—Sketch from a longitudinal section through the area indicated by arrows in figure 2, showing the absence of muscularis (represented by the solid black) over the incised pylorus.

splitting of the pylorus. As will be noted in the protocol and chart of this animal, incisions over the prepyloric antrum and duodenum were without effect, only after the pyloric sphincter was successfully cut did the usual drop in the neutralization curve take place (fig 4). The

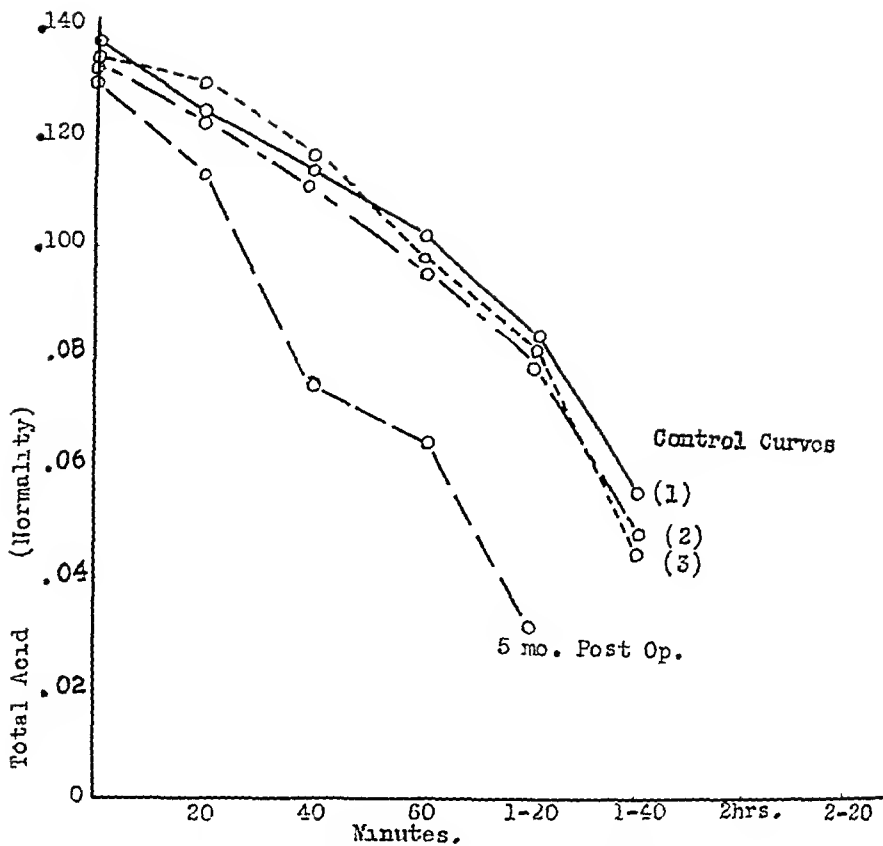


Fig 4—Neutralization curves for dog 161, weighing 11 Kg Control curves (1, 2 and 3) show the absence of any effect of incisions over the prepyloric antrum and duodenum The curve five months after splitting of the pyloric sphincter is shown below Autopsy showed a good pout at the site of incision (see protocol in text)

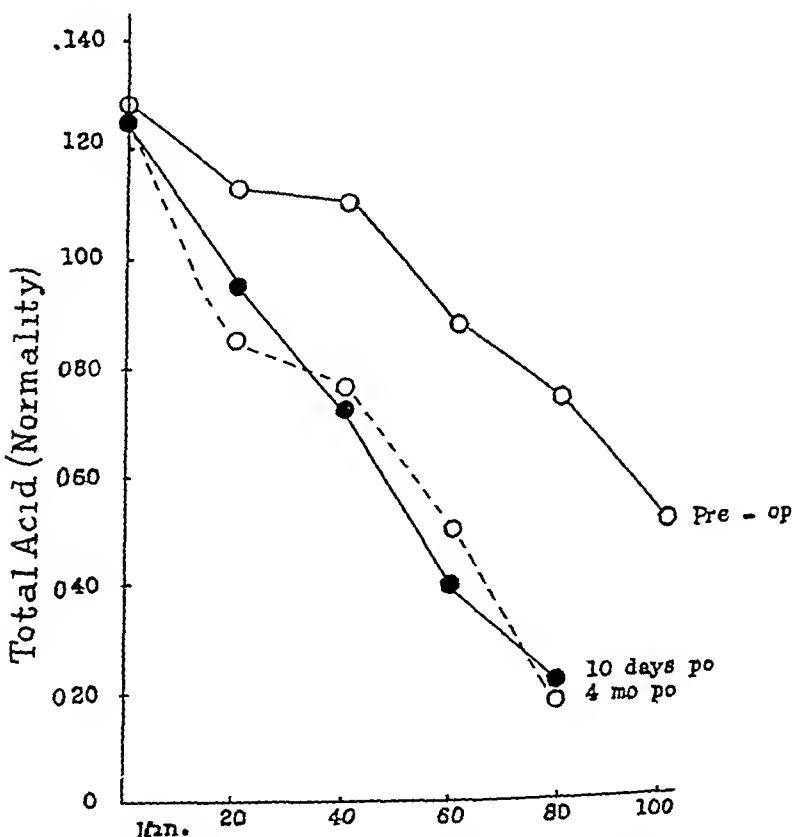


Fig 5—Neutralization curves for dog B14, weighing 9 Kg Accidental death occurred five months after operation Autopsy showed no adhesions and a good pout of the submucosa through the incision Figure 6 shows a cross-section through the pylorus



Fig 6—Sketch from a cross-section of the pylorus in dog B14, showing the absence of muscularis (represented by the solid black) over the incised pylorus

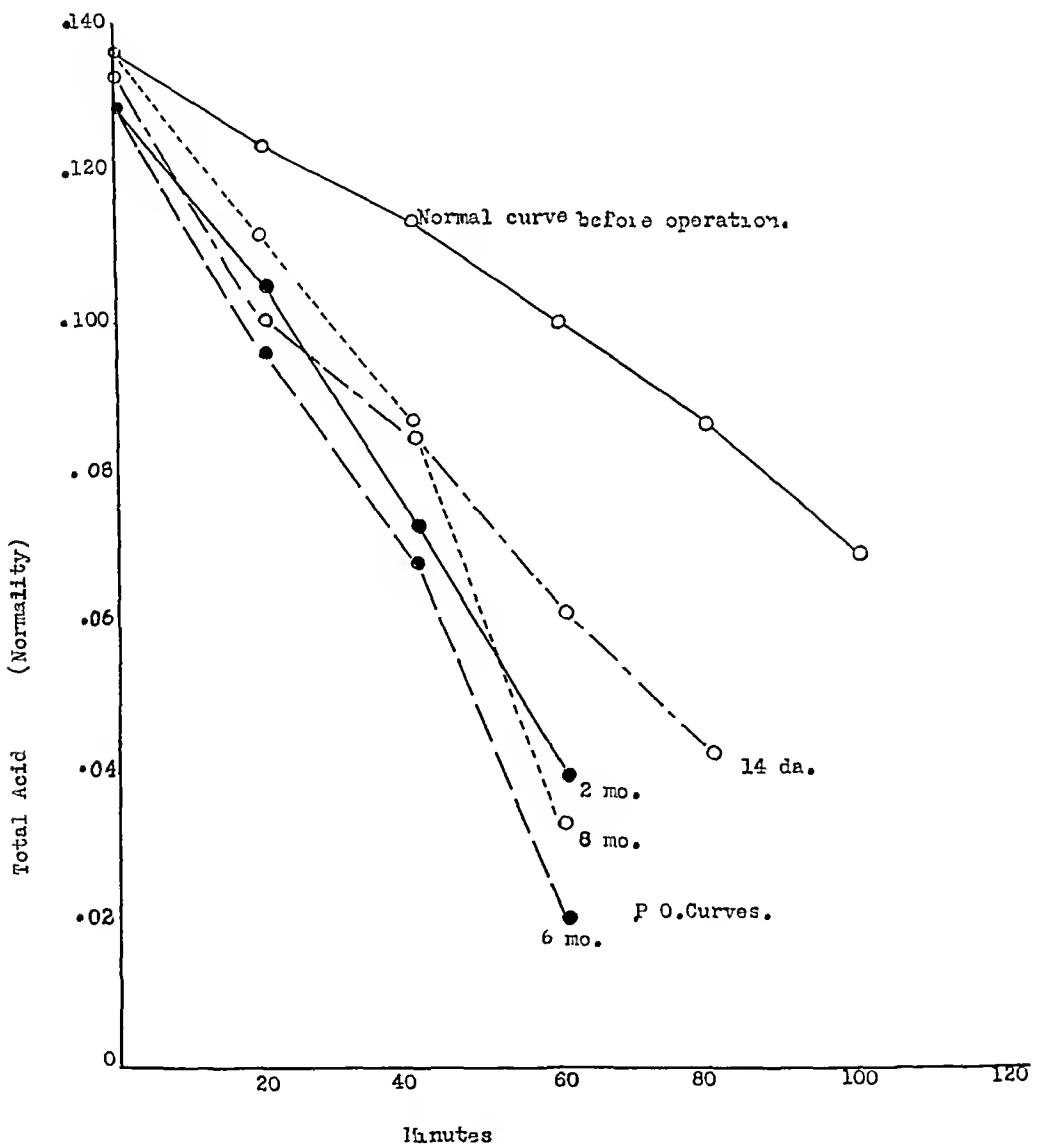


Fig 7—Neutralization curves for dog 303, weighing 11 Kg, killed six months after operation because of extensive involvement of the skin with mange Autopsy showed a good pout and no adhesions Figure 8 shows the gross specimen cut open

observations at autopsy in this dog are also of special interest, and a protocol will therefore be given

Dog 161, a black female, weighed 11 Kg. The neutralization test made before operation showed the usual curve (curve 1, fig 4). On Feb 19, 1929, a longitudinal incision about 2 inches (5 cm) long was made on the anterior surface of the prepyloric antrum from the incisura to the beginning of the pylorus. The submucosa pouted into the opening, which was covered with omentum. One month later another test showed no change (curve 2, fig 4). At a second operation the prepyloric incision was found intact, not adherent, with no scarring across its edges. An incision was made along the duodenum distal to the pylorus and covered with omentum. Curve 3 in figure 4 shows no change several weeks later. The dog was not observed over the summer months, but on September 25



Fig 8—Photograph of gross specimen from dog 303. The lumen of the specimen was filled with water before fixation, and then the anterior wall was cut away. The arrows indicate the incised part of the pylorus. Sections of this area show the same picture as represented in figure 3.

showed no alteration in the neutralization curve (not shown in fig 4). At operation the next day the pyloric sphincter was carefully cut across as described. This time there was a decided drop in the neutralization curve on repeated tests after operation. The curve obtained at five months is represented in figure 4. Shortly afterward the dog showed signs of gastric irritability and vomited; it was found dead on March 16, 1930. Autopsy revealed a good pout through the pyloric incision, with no adhesions around it except to the protecting layer of omentum. The prepyloric and duodenal incisions had both healed with little trace. The pancreas was hard and white and had several areas of fat necrosis in its capsule and a few in the surrounding mesentery. When the duodenum was opened, a small perforating ulcer was found on its posterior wall just distal to the pylorus which opened into a small cavity full of tangled hair.

COMMENT

The observations herein reported indicate that gastric acidity is more rapidly neutralized and the gastric emptying time somewhat reduced consequent to successful division of the pyloric sphincter, and that this effect persists as long as ten months, or the duration of the observations. It does not seem unfair to infer that the removal or diminution of this barrier renders the stomach more readily accessible to duodenal contents, notably alkaline pancreatic juice, which is thus more easily regurgitated, augments neutralization and makes for a low gastric acidity. If this is true, the theory may be advanced that gastric acidity may be regulated by the pylorus rather than vice versa, i. e., that one may perhaps speak of the pyloric control of gastric acidity.

It is, of course, possible that these observations may be explained in another way. Thus, one may suppose that the acid solution is more rapidly neutralized in these experiments because it is being discharged from the stomach more rapidly, assuming that factors within the stomach are wholly responsible for its neutralization, and there is, thus, much less of the acid to neutralize. From an examination of our data, however, the increased emptying time is not always a prominent feature of the change and, indeed, in some of the experiments did not occur.

More significant, however, is the fact that the existence or at least the importance of these intrinsic gastric factors has not been amply demonstrated. Mucus, for example, was observed in these experiments only in the last samples and often not at all. The secretion by the stomach of a neutral chloride which lowers gastric acidity by dilution is assumed by MacLean and Griffiths¹⁷ on the basis of many special fractional test meals in man. This idea is similar to Pavlov's old assumption of a "Verdunnungssaft," an idea which fell by the wayside because of insufficient support.³ The most significant facts indicating that intrinsic gastric factors probably play but a minor rôle are that they fail to operate under so many experimental conditions. Thus, it has been shown that neutralization does not take place when the pylorus or pancreatic ducts are tied, is slowed in partial pyloric obstruction, and is absent when the pancreatic juice is drained to the outside.¹⁸

The present observations would seem to account for the frequent association between anacidity and a patulous pylorus, the latter favoring reflux of pancreatic juice and thus explaining the former. It brings up the question of the cause of anacidity so frequently found in, and often considered essential to, the diagnosis of gastric carcinoma. That this is scarcely due to absence of secretion is shown by the frequent finding of great stretches of normal appearing and staining gastric

17 MacLean, H., and Griffiths, W. J. *J. Physiol.* **66** 356, 1928.

18 Elman (footnote 1, first and second references) Babkin (footnote 3)

mucous membrane at autopsy even when large parts of the organ are involved in the new growth. Nor is the finding of anacidity invariable. We have seen several cases recently in which normal acidity was present. In several patients with proved carcinoma of the stomach, too few to draw general conclusions, one of us (R. E.) has obtained very rapid neutralization curves after "acid test meals," which suggests that either a patulous pylorus may account for the anacidity or that the growth acts as a splint to the muscle preventing contraction and thus promoting duodenal regurgitation. The delayed emptying of the stomach frequently noted on roentgen examination of cases of gastric carcinoma does not necessarily preclude this idea, because if the wall of the stomach is splinted by the growth it cannot empty adequately. Recently, Hughson,¹⁹ by "splinting" the pylorus in a special way, was able to show an increase in the healing of experimental ulcers, though unfortunately he made no studies of gastric acidity.

If the pylorus plays an important rôle in regulating gastric acidity, it explains the frequent observations of hyperacidity in cases with dynamic pylorospasm from ulcer or reflex causes, and emphasizes the importance of this structure in the cure of such conditions. It is of interest to note that in a recent paper by Einhorn²⁰ several patients, poor surgical risks, are reported as greatly relieved from symptoms of duodenal ulcer by stretching of the pylorus without operation. This was done by having the patient swallow a collapsed balloon which was then allowed to pass into the duodenum. The balloon was then sufficiently inflated and pulled back through the pylorus. Analogous to this, perhaps, is the relief often seen following manual dilatation of a spastic sphincter and both in promoting colonic motility and in the healing of fissures of its mucous membrane. Experiments are now in progress attempting to produce a condition of increased pyloric activity. In one such experiment in which a circular ligature was placed around the pylorus—insufficient to cause obstruction, but presumably enough to prevent full relaxation—a definite delay in neutralization was demonstrable.

The observations on dog 161 (see protocol) deserve special mention, for they illustrate anew the rôle of the pancreatic juice as well as of the pyloric sphincter in protecting the duodenum from the insults of acid gastric juice and have suggestive bearings on the question of the pathogenesis of duodenal ulcer. In a previous paper²¹ from this laboratory

19 Hughson, Walter. Relation of the Pylorus to Duration of Experimental Gastric Ulcer, *Arch Surg* **15** 66 (July) 1927.

20 Einhorn, Max. *M J & Rec* **131** 285, 1930.

21 Elman, Robert, and Hartmann, A. F. The Cause of Death Following Rapidly the Total Loss of Pancreatic Juice, *Arch Surg* **20** 333 (Feb) 1930.

the finding of such lesions following persistent drainage of the pancreatic juice to the outside was noted. In this experiment a similar absence of this alkaline secretion occurred by spontaneous disease of the gland. The insufficient sphincter presumably aggravated the condition by allowing acid gastric juice free access to the unprotected duodenum. This suggests the conception of an adequate preparation of gastric contents for reception by the duodenum, which has been convincingly elaborated by Apperly²² on the basis of his own observations, and which is receiving increasing support. That its failure may have something to do with the genesis of duodenal and even gastrojejunal ulcers is a theory for which considerable evidence exists.

SUMMARY

Experiments are described in which successful division of the pyloric sphincter was achieved and which as a consequence show a persistent lowering of gastric acidity as measured by an augmented neutralization of an "acid test meal." A moderate increase in the emptying time was also observed. Inferences from this and other evidence seem to justify the conception of "the pyloric control of gastric acidity" rather than that of unqualified acid control of the pylorus. Certain clinical implications are discussed.

²² Apperly, F. E. *Brit. J. Exper. Path.* **7** 111, 1926.

PYLORIC BLOCK

WITH SPECIAL REFERENCE TO THE MUSCULATURE MYENTERIC
PLEXUS AND LYMPHATIC VESSELS

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ROCHESTER, MINN.

MUSCULATURE AND MYENTERIC PLEXUS

One of the interesting facts about the physiology of the gastro-intestinal tract is that peristaltic waves coursing over the stomach seem to stop at the pylorus or a few centimeters above it. Many investigators (Joseph and Meltzer,¹ Wheelon and Thomas,² Alvarez and Mahoney,³ Payne and Poulton⁴ and Ivy and Vloedman⁵) have frequently observed tonus waves in the duodenum as the gastric wave approached the pylorus. At times it seems as if the gastric waves actually jump the pyloric barrier and extend down the duodenum as peristaltic rush waves (Alvarez⁶). And yet, the best evidence points to the fact that the duodenal waves originate in the first part of the duodenum and are not propagated gastric waves which have jumped the pyloric barrier (Cole⁷ and Alvarez). Why do not the gastric waves go on down the bowel, and why are they blocked at the pylorus? It has been suggested that the block may be due to the anatomic peculiarities in this region or to

* Submitted for publication, March 17, 1930.

¹ From the Division of Medicine, the Mayo Clinic.

² Work done in the Section on Pathologic Anatomy, the Mayo Clinic. In this paper is reported the greater part of the work for which the John Horslev Memorial Prize for 1929 was awarded by the University of Virginia. The remainder appeared in the *American Journal of Anatomy* (61:197, 1928).

1. Joseph L. R., and Meltzer, S. G. Inhibition of the Duodenum Coincident with the Movements of the Pyloric Part of the Stomach, *Am. J. Physiol.* 27:31 (Feb.) 1911.

2. Wheelon, H., and Thomas, J. L. Observations on the Mobility of the Duodenum and the Relation of Duodenal Activity to that of the Pars Pylorica, *Am. J. Physiol.* 59:72 (Feb.) 1922.

3. Alvarez, W. C., and Mahoney, Lucille J. The Relations Between Gastric and Duodenal Peristalsis, *Am. J. Physiol.* 64:371 (April) 1923.

4. Payne, W. W., and Poulton, E. P. Visceral Pain in the Upper Alimentary Tract, *Quart. J. Med.* 17:53 (Oct.) 1923.

5. Ivy, A. C., and Vloedman, D. A. The Small Intestine in Hunger, *Am. J. Physiol.* 72:99 (March) 1925.

6. Alvarez, W. C. The Mechanics of the Digestive Tract, ed. 2, New York: Paul B. Hoeber, Inc., 1928, pp. 447.

7. Cole, L. G. Motor Phenomena of the Stomach, Pylorus and Cap Observed Roentgenographically, *Am. J. Physiol.* 42:618 (March) 1917.

the physiologic differences that exist between the muscle in the pyloric antrum and that in the duodenum. Of the many descriptions of the anatomic structure of the stomach in man, there are relatively few concerning the block at the pylorus and the relationship of the circular and longitudinal fibers in this area to those of the duodenum, and there are no references, so far as I am aware, regarding the continuity of the myenteric plexus. In Morris' "Human Anatomy"⁸ (seventh edition) it is stated that the circular fibers of the stomach are continuous with the circular fibers of the duodenum, while in Gray's "Anatomy of the Human Body"⁹ (twentieth edition) it is stated that the circular fibers of the stomach are not continuous with those of the duodenum. These volumes contain little regarding the other structures in this area. Furthermore, practically nothing is known about the generic and individual variations in this area, either in the lower animals or in man. And yet, "probably no portion of the digestive tube bears so close a relation to all diseases of the stomach and duodenum, as does the pylorus itself. And there is probably no field in the whole subject of medicine about which we have so little absolute knowledge as that of the neurology of the gastro-intestinal tract" (Hughson¹⁰). Alvarez and Mahoney (1923) emphasized the importance of additional research in this field.

This study was primarily undertaken with the hope of determining the percentage of circular and longitudinal fibers in the pars pylorica that are continuous with the circular and longitudinal fibers of the duodenum (table), and also to determine, if possible, some of the individual variations that occur in this region. The results, with a review of the literature, have been published (Horton¹¹). Therefore, in this paper I shall point out only one possibility that has to do distinctly with the musculature, which was not included in the previous paper. Hypertrophic pyloric stenosis is occasionally observed in the new-born infant and may well be explained by the data represented in figures 1 and 2. Figure 1 represents a section through the pylorus of a male fetus of 6½ months, and figure 2 represents a section through the pylorus of a full term male fetus. The ratio of the thickness of the muscle wall to the lumen may be noted in the two figures. Persistence of the thickened muscle in figure 1 may explain the occurrence of

8 Morris, Henry. Human Anatomy, ed 7, Philadelphia, P. Blakiston's Son & Company, 1923, pp 1507.

9 Gray, Henry. Anatomy of the Human Body, ed 20, Philadelphia, Lea & Febiger, 1918, p 1165.

10 Hughson, Walter. Reflex Spasm of the Pylorus and its Relation to Diseases of the Digestive Organs, Arch Surg **11** 136 (July) 1925.

11 Horton, B. T. Pyloric Musculature with Special Reference to Pyloric Block, Am J Anat **61** 197 (May) 1928.

Micrometer Measurements of Microscopic Sections of Pylorus, Showing Percentage of Circular and Longitudinal Muscle Fibers Crossing from Stomach to Duodenum

Case	Age, Years	Sex	Sections Measured	Stain		Continuity of Musculature, per Cent	
				Hematoxylin and Eosin	Van Gieson	Circular	Longitudinal
1	20 days	F	10		10		13.0
2	28 days	F	1,210*		1,210	0.12	21.4
3	4 months	F	126		126		10.8
4	6 months	M	150		150		53.0
5	8 months	M	150	15	135		23.0
6	11 months	M	16	8	8		56.0
7	1	M	445†		445		24.0
8	2	M	79		79		61.0
9	2½	F	12		12		
10	4	F	20		20		26.4
11	4	F	46		46		45.1
12	16	F	12	6	6		4.0
13	17	M	10	5	5		43.5
14	19	M	11	4	7		30.0
15	19	F	4		4		35.0
16	21	F	14	5	9		11.5
17	21	F	10	5	5		30.0
18	22	M	8	4	4		7.5
19	23	F	12	4	6		28.0
20	23	M	4		4		41.7
21	26	F	11	5	6		40.0
22	29	M	15	7	8		6.9
23	32	M	13	6	7		42.5
24	32	M	10	5	5		40.0
25	34	F	4		4		10.5
26	35	M	17	8	9		21.0
27	36	M	12	4	8		20.0
28	36	F	10	5	5		9.9
29	37	F	13	6	7		22.5
30	39	M	10	5	5		46.5
31	40	M	10	5	5		66.0
32	40	F	14	7	7		18.8
33	41	M	11	5	6		18.0
34	42	F	9	5	4		8.6
35	42	F	19	8	11		17.0
36	42	M	13	5	8		17.9
37	43	M	13	7	6		8.6
38	43	F	117	9	108		47.0
39	43	F	8	4	4		5.0
40	43	F	13	7	6		10.0
41	43	F	5		5		45.0
42	44	M	9	5	4		37.0
43	45	F	8	4	4		43.0
44	45	F	13	5	8		24.0
45	45	M	12	6	6		37.0
46	45	M	12	5	7		23.0
47	46	F	10	6	4		45.6
48	47	M	12	6	6		10.0
49	48	F	16	8	8		52.0
50	48	F	12	6	6		17.2
51	48	F	10	6	4		16.2
52	49	M	14	7	7	0.5	12.3
53	50	F	8	4	4		7.5
54	51	F	15	6	9		2.6
55	51	F	10	5	5		14.2
56	53	F	11	5	6		25.7
57	53	M	12	6	6		22.4
58	54	M	13	7	6		26.2
59	55	M	17	8	9		16.4
60	55	M	10	5	5	2.0	33.0
61	55	F	8	4	4		23.5
62	55	F	9	5	4		19.6
63	56	F	11	6	5		12.0
64	59	M	10	4	6		40.0
65	62	F	11	4	7		21.0
66	62	M	12	6	6		5.8
67	62	F	11	7	6		4.5
68	64	M	8	4	4		25.0
69	65	M	11	6	5		13.0
70	67	M	10	5	5		7.9
71	67	F	11	5	6		7.2
72	67	F	12	6	6		26.8
73	69	F	10	5	5		7.0
74	69	M	10	5	5		24.0
75	70	M	22	12	13		15.2
76	70	F	13	7	6		25.5
77	71	M	5		5		22.8
78	72	M	8	4	4		4.6
79	73	M	12	6	6		10.2
80	74	M	19	8	11		12.9
81	74	M	14	5	7		11.0
82	74	M	9		4		7.0
83	75	M	4		4		22.0
84	76	M	4		4		41.0

* Each of 1,210 sections in this series was measured
† Of the 1,335 sections in this series, every third section was measured

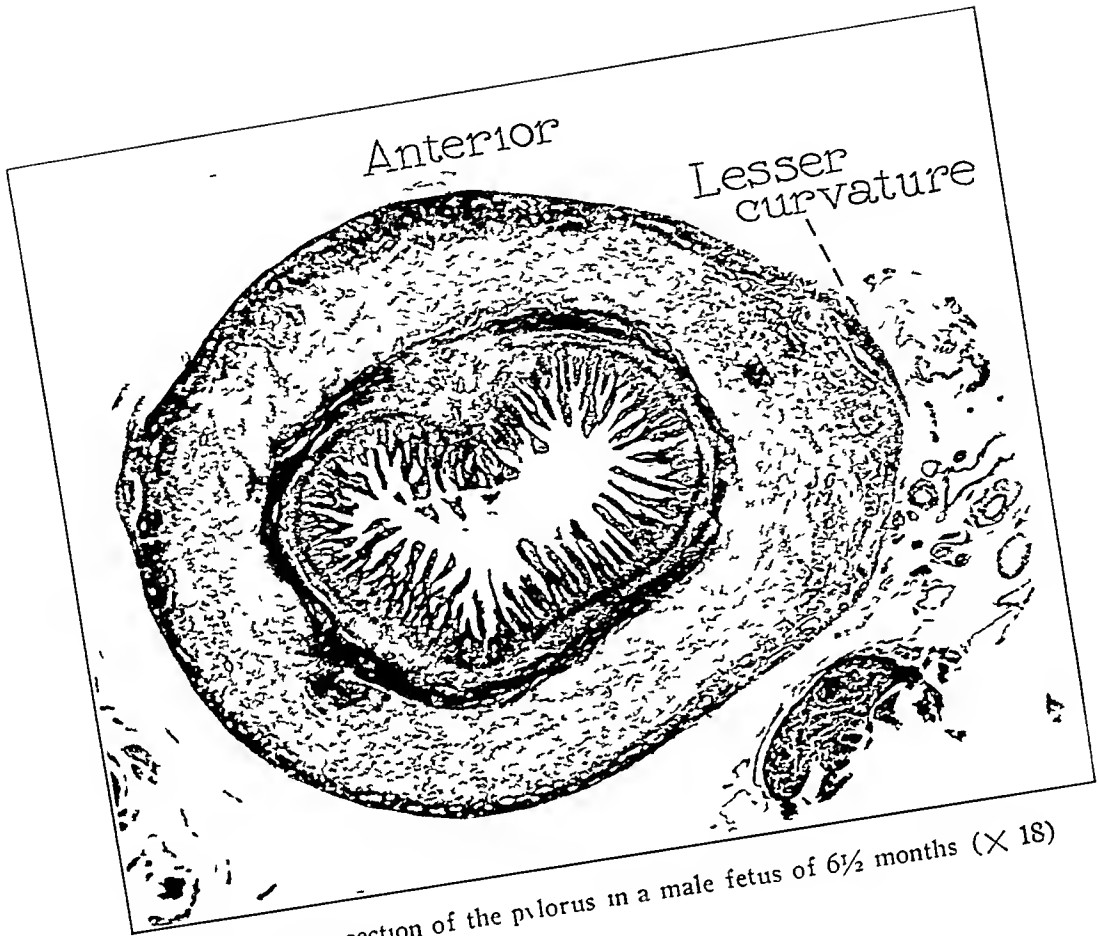


Fig 1—Cross-section of the pylorus in a male fetus of 6½ months (× 18)

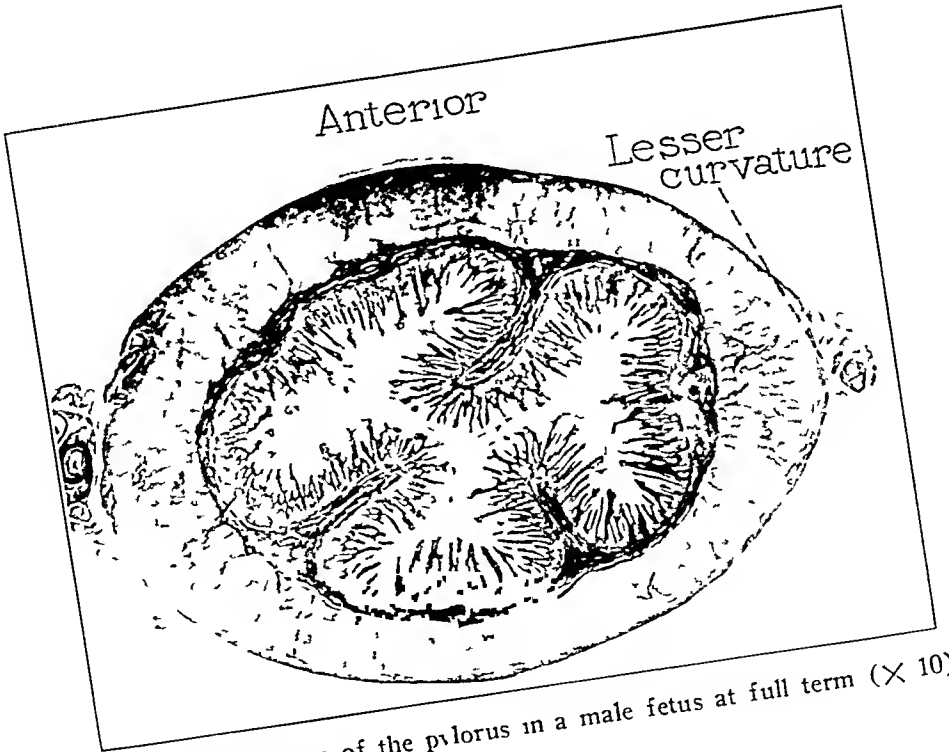


Fig 2—Cross-section of the pylorus in a male fetus at full term (× 10)

hypertrophic pyloric stenosis at birth. From a study of embryonic and fetal stomachs, a relatively thick pylorus at the fifth to sixth month of development is a usual observation.

As the work developed, I soon realized that other structures at the pylorus would be just as interesting to the investigator, and as a result, the problem was broadened to include a study of the myenteric plexus and the lymphatic vessels. Williams,¹² working in the same laboratory with me, has since demonstrated an almost complete block in the anastomosis of intramural arteries across the pyloric sphincter.

Review of the Literature—Auerbach,¹³ in 1862, first described the nerve plexus that bears his name. Since that time many investigators have contributed to the knowledge of the subject (Cajal,¹⁴ Kolliker,¹⁵ Dogiel,¹⁶ Muller¹⁷ and Kuntz¹⁸), but there are no references in the literature, so far as I am aware, regarding the continuity of the myenteric plexus (Auerbach's plexus) from the stomach to the duodenum. Dr Kuntz,¹⁹ professor of anatomy at St. Louis University, stated that he knew of no work on the subject, and yet he has been interested in the autonomic nervous system for the last twenty-one years and has contributed many excellent articles to the literature. Other anatomists (Dr R. E. Scammon,²⁰ of the University of Minnesota, and Dr H. A. Harris,²¹ at the University College of London) have made similar statements. Hill,²² in a recent article, gave the best review of the literature on the myenteric plexus, but made no statement regarding

12 Williams, T. B. Vascular Studies of the Pylorus, *Anat. Rec.* **38** 273 (May) 1928.

13 Auerbach, L., quoted by Oppel, Albert. *Lehrbuch der vergleichenden mikroskopischen Anatomie der Wirbeltiere*, Jena, Gustav Fischer, 1896, vol. 1, p. 27.

14 Ramon Cajal, S., quoted by Kuntz, Albert. *J. Comp. Neurol.* **23** 173 (June) 1913, quoted by Hill, C. J. *Philos. Tr.*, London **215** 355 (Jan.) 1927.

15 Kolliker, Albert. *Ueber die feinere Anatomie und die physiologische Bedeutung des sympathischen Nervensystem*, Vienna, Wilhelm Braumüller, 1894, p. 24.

16 Dogiel, A. S., quoted by Kuntz, Albert. *J. Comp. Neurol.* **23** 173 (June) 1913, quoted by Hill, C. J. *Philos. Tr.*, London **215** 355 (Jan.) 1927.

17 Muller, L. R., quoted by Kuntz, Albert. *J. Comp. Neurol.* **23** 173 (June) 1913.

18 Kuntz, Albert. On the Innervation of the Digestive Tube, *J. Comp. Neurol.* **23** 173 (June) 1913.

19 Kuntz, Albert. Personal communication to the author.

20 Scammon, R. E. Personal communication to the author.

21 Harris, H. A. Personal communication to the author.

22 Hill, Catherine J. A Contribution to Our Knowledge of the Enteric Plexus, *Philos. Tr.*, London **215** 355 (Jan.) 1927.

this plexus at the pylorus Lataret,²³ Brandt²⁴ and McCrea²⁵ stated that the vagal fibers extend up to the pylorus, but do not cross it. The literature regarding the innervation of the pyloric sphincter is confusing. Many workers contend that vagal influence is for contraction and sympathetic influence is for relaxation, while others maintain the reverse of this hypothesis. The best evidence seems to support the former view.

Methods and Material Studied—The material used in this study, as set forth in a previous paper (Horton,¹¹), was obtained from postmortem examinations at the Mayo Clinic.

For the study of the myenteric plexus, blocks of tissue were taken from six normal stomachs at points 1, 2, 3 and 4, as shown in figure 3. They were obtained from subjects aged less than 1 year. Serial sections 10 microns thick were made from each block. They were cut parallel with the long axes of the pyloric canal and extended from 5 to 8 mm into the duodenum. A modification of the Orlandi stain, which Kernohan²⁶ has described, and the van Gieson stain were used to

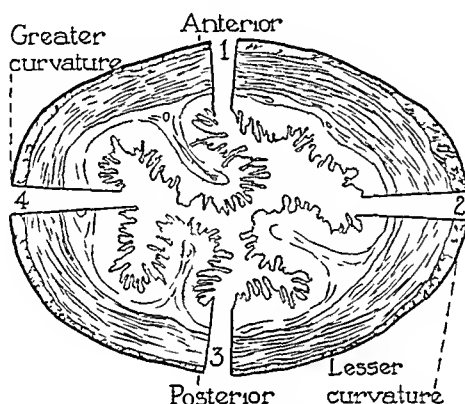


Fig 3—Cross-section of the pyloric canal in a full term fetus about 1 cm above the pyloric sphincter

bring out the myenteric plexus. By means of a projectoscope, the microscopic picture was projected on a screen, and areas of nerve tissue, together with an outline of the mucosa and musculature, were traced on paper and transferred to thin glass plates. Enamel paint and india ink were used to make the drawings on the glass plates. A definite color was used to represent each structure transferred to the plates, and this color scheme was carried out in all of the reconstructions. From twenty-five to sixty microscopic sections from a given serial, taken in consecutive order, were traced on glass plates, and the plates stacked in consecutive order. With a strong light behind the stack of plates, an excellent picture is obtained. When the glass plates are accurately superimposed in consecutive order, the various elements of the myenteric plexus form a continuous,

²³ Lataret, A, quoted by Hughson, Walter. *Arch Surg* **11** 136 (July) 1925.

²⁴ Brandt, W. Die Innervation des Magens, *Ztschr f ang Anat* **5** 302, 1920.

²⁵ McCrea, E. D. The Abdominal Distribution of the Vagus, *J Anat* **59** 18, 1924.

²⁶ Kernohan, J. W. Adaption of Bielschowsky's Silver Impregnation Method for Material Imbedded in Paraffin or Celloidin, to be published.

although winding, chain from the stomach to the duodenum. This method of using glass plates has not been used at the Mayo Clinic before, and at the time I devised the method I had not found a reference to it in the literature.

Results—The myenteric plexus is continuous from the stomach to the duodenum, as shown in figures 4, 5, 6 and 7. This was true in all of the cases studied. Reconstructions from various segments of the pyloric ring showed variations in the appearance of the ganglionic chain, but these variations seemed to be due to the irregularity in arrangement of the muscle fibers in this area. The ganglia of the myenteric plexus are irregular aggregates of neurons interposed between the circular and longitudinal muscle coats and are connected with each

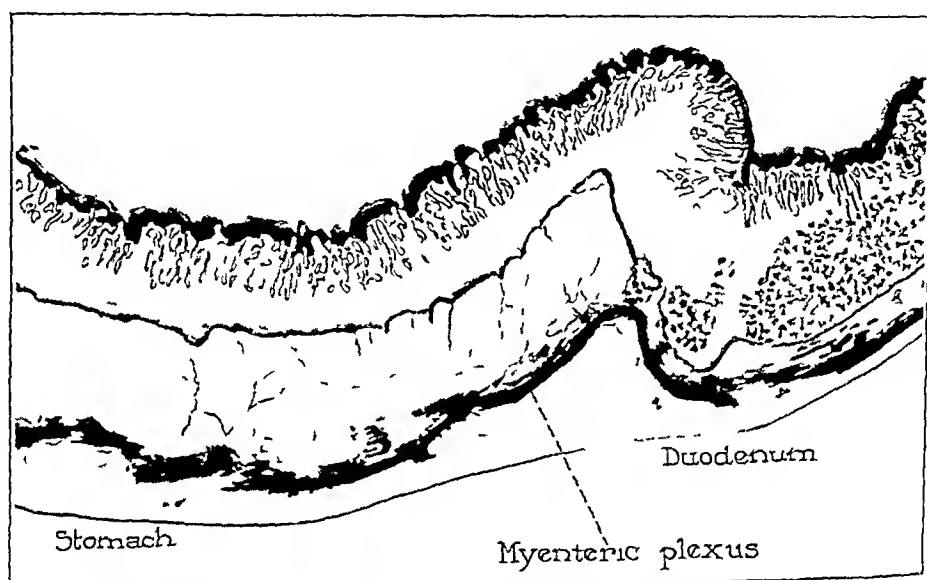


Fig. 4—Reconstruction of the myenteric plexus, showing the continuity from the stomach to the duodenum. This is a drawing of a glass model that was made from twenty-nine serial sections. It represents a longitudinal block through point 4 in figure 3. The subject was a boy, aged 8 months.

other by bundles or bands of nonmedullated nerve fibers. The ganglia of the submucous plexus are much smaller collections of neurons, connected in a similar manner, although in many sections it is difficult, and frequently impossible, to trace the connections. The connections between the two plexuses are frequently easy to trace, and it would seem from the histologic structure that the submucous plexus represents a subdivision of the larger myenteric plexus. Fine fibrils from the submucous plexus can be seen to terminate on or adjacent to the epithelial cells lining the digestive tube, while the fibrils from the myenteric plexus can frequently be seen to terminate on muscle cells.

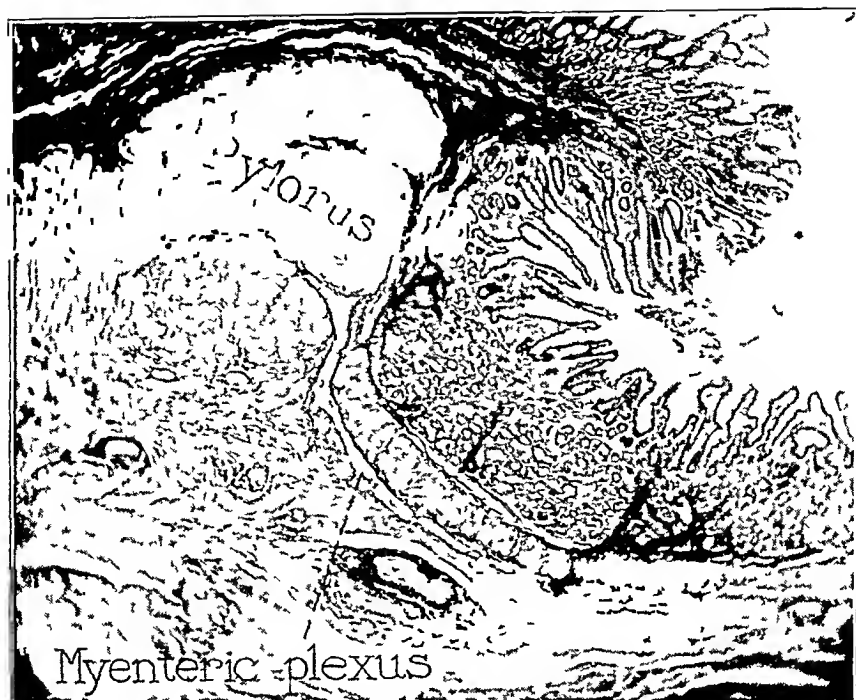


Fig 5—Longitudinal section through the pylorus, showing the myenteric plexus between the circular and the longitudinal muscle, in the duodenopyloric juncture in a female subject, aged 4 weeks ($\times 25$)

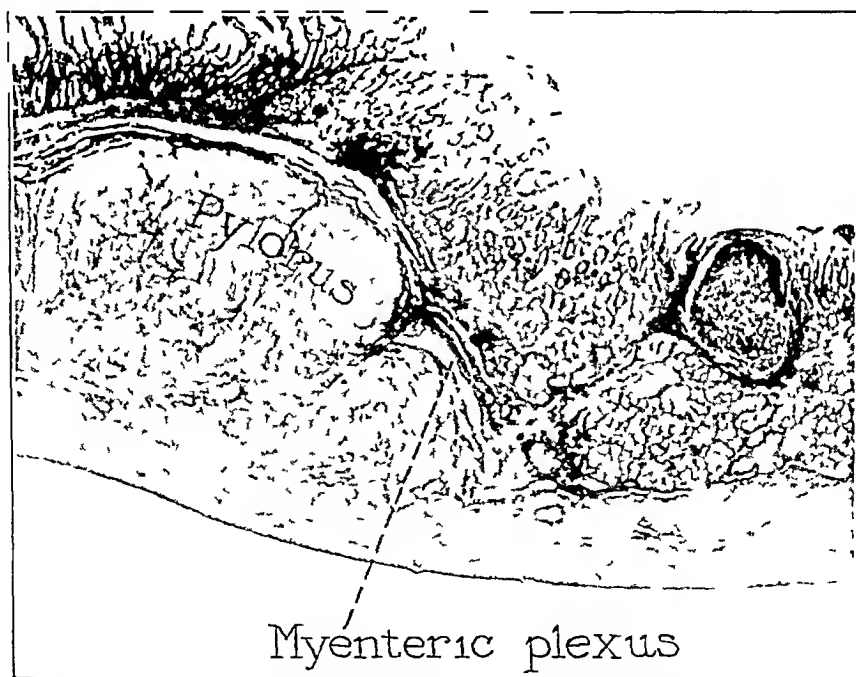


Fig 6—Longitudinal section through the pylorus showing the myenteric plexus in the submucosa at the duodenopyloric juncture in a male subject, aged 1 year ($\times 22$)

The myenteric plexus was normally found between the circular and the longitudinal muscle coats (fig 5), but in one specimen (figs 6 and 7) the continuity of the myenteric plexus from the stomach to the duodenum was by way of the submucosa. In this specimen, at the duodenopyloric juncture, the myenteric plexus (Auerbach's plexus) occupied the position normally occupied by the submucous plexus (Meissner's plexus). This is probably a fairly normal occurrence in this area, and perhaps definite significance cannot be attached to the observation. Reconstructions of Meissner's plexus have not been made.

Comment—It is apparent from the results of this study that there is an almost complete separation between the circular muscle of the

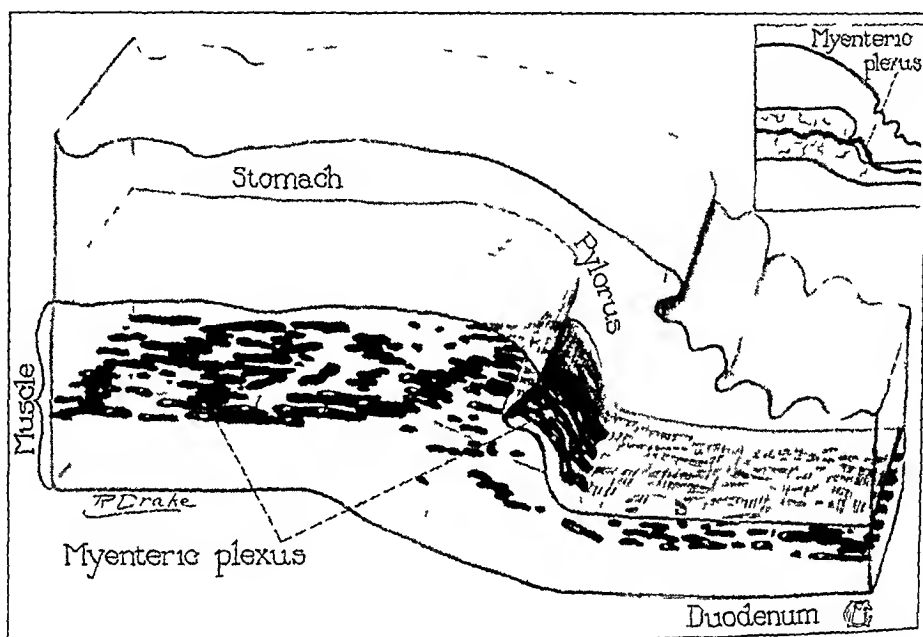


Fig 7—Reconstruction of the myenteric plexus illustrated in figure 6, showing the continuity from the stomach to the duodenum by way of the submucosa. The drawings are of a glass model, which was made from sixty serial sections. It represents a longitudinal block through point 2, figure 3. The insert is the view one obtains when looking down through the model from above. The subject was a boy, aged 1 year.

stomach and the duodenum, an interruption of continuity with physiologic significance, as Cannon²⁷ expressed it, and partial block of the gastric longitudinal fibers. The interruption of the circular muscle at the duodenopyloric juncture undoubtedly accounts for the block in peristaltic waves at the pylorus. The changes in tonus that are frequently observed in the duodenum, with the approach of gastric waves, are probably due to the spread of some influence along the myenteric plexus,

²⁷ Cannon, W. B. *The Mechanical Factors of Digestion*, London, E. Arnold 1911, p. 227.

or along the narrow bridges of muscle connecting the stomach and duodenum, or perhaps along both routes. If the gastric waves were not blocked at the pylorus, but traveled on down the duodenum, even for a short distance, duodenal ulcer would probably become much less common than at present.

As has already been written (Horton¹¹), in the distal portion of the pyloric canal, where most of the longitudinal fibers dip into the circular muscle (to form the dilator muscle of the pylorus), it would certainly seem, from the anatomic arrangement of these fibers, that they must act as a dilator of the pylorus. The marked hypertrophy of these fibers, unassociated with hypertrophy of the circular fibers, which I have observed in annular carcinoma of the pyloric canal with partial obstruction to the pyloric outlet tends to substantiate this view.

LYMPHATIC VESSELS OF THE STOMACH WITH SPECIAL REFERENCE TO PYLORIC BLOCK

Carcinoma of the stomach rarely invades the duodenum. It apparently spreads easily in all directions in the walls of the stomach and often extends to the pyloric ring, but it seems to stop there abruptly. Even in advanced cases, the duodenum may remain free. It is well known that carcinoma usually spreads by direct extension or by way of the lymphatic system. Is there a barrier at the pylorus to the spread of carcinoma? If so, what is the nature of this barrier? Several theories have been advanced in explanation of the immunity of the duodenum. It has been attributed to scarcity of lymphatic vessels between the two organs, to the upward flow of lymph from the duodenum to the stomach, to the alkalinity of the duodenum and to the obliteration of tissue spaces by spasmodic contraction of the pyloric sphincter so as to form a mechanical obstruction to the advance of the carcinoma. I shall consider here the lymphatic drainage of the stomach, the relationship between the lymphatic vessels of the stomach and those of the duodenum and their bearing on the problem.

Review of the Literature—Excellent historical reviews of the lymphatic system are given by Todd,²⁸ Cruveilhier,²⁹ Hewson³⁰ and Poirier, Cuneo and Delamere³¹. According to the latter authors, Herophilus

28 Todd, R. B. The Cyclopaedia of Anatomy and Physiology, London, Longman, Brown, Green, Longmans and Roberts, 1839-1847, vol. 3, p. 205.

29 Cruveilhier, Jean. The Anatomy of the Human Body, New York, Harper & Brothers, 1844, p. 907.

30 Hewson, William. A Description of the Lymphatic System, London, The Sydenham Society, 1846, p. 119.

31 Poirier, P., Cuneo, B., and Delamere, Gabriel. The Lymphatics, London, Constable & Company, 1913, p. 301.

(300 B C) and Erasistratus (280 B C) should be accorded the honor of discovering the chyliferous vessels. But Todd, Cruveilhier and Hewson³² did not mention any of the writers before Galen, and Todd and Cruveilhier gave Eustachius (1453), who described the thoracic duct in the horse, the honor of discovering the lymphatic system. Sixty-nine years later, Gaspard Asellius (1622), while seeking another object discovered, on the mesentery of a dog, certain vessels that were carrying a milk-like fluid, he called these vessels lacteals. He died in 1626 without ever seeing the lacteals in man. Pecquet (1641) discovered the receptaculum chyli and showed that the lacteals entered the thoracic duct, and not the liver, as Asellius and his contemporaries believed. Rudbeck (1651) described the lymphatics of the liver, the pancreas, the lungs and the pelvis and concluded from his researches that the "serous vessels" existed throughout the organism and formed a special system. Bartholin, in Denmark, and Jolyffe, in England (about 1652) confirmed Rudbeck's attempt at generalization, and the "serous system" became the lymphatic system. In 1654, the function of absorption was ascribed to this system by Glisson and Hoffmann. After this period Nuck added to the knowledge of this system by injection of the lymphatic glands, Ruysch by his description of the valves of the lymphatic vessels and Meckel by his accurate account of the whole system. Other workers (Albinus, Hunter, Monro, Hewson, Cruikshank and Mascagni) added various details concerning the system. Several years later, Lippi (1822) and Lauth (1824) discovered the existence of peripheral lymphatic venous communications. In 1847, Sappey³³ began his researches which he continued until the publication of his atlas in 1876. Following Sappey, the chief work on the lymphatics of the stomach has been done by Most (1899), Cuneo (1900), Cuneo and Delamere (1900), Polya and von Navratil³⁴ and Jamieson and Dobson³⁵. Very little work has apparently been done on the lymphatics of the stomach during the last twenty years. In fact, I have looked through all the volumes of the *Quarterly Cumulative Index Medicus* twice, without finding a single reference dealing with the injection of lymphatics of the stomach. Most textbooks on anatomy state that there are two main areas of lymphatic drainage in the stomach: the one along the lesser curvature and the other

32 Hewson added in a footnote that the lacteals had been seen in kids by Erasistratus, who called them arteries. Hewson really gave Asellius the main credit for the discovery of the lymphatic system.

33 Sappey, C. Cited by Poirier. Cuneo and Delamere (footnote 31).

34 Polya, Eugen, and von Navratil, Desider. Untersuchung über die Lymphbahnen des Wurmfortsatzes und des Magens, *Deutsche Ztschr f Chir* 69:421 (Aug) 1903.

35 Jamieson, J. K. and Dobson, J. F. Lectures on the Lymphatic System of the Stomach, *Lancet* 1:1061 1907.

along the greater curvature. The latter is usually divided into two groups, one draining toward the subpyloric group of lymph nodes and the other to the splenic lymph nodes. A few (Gray's anatomy and Cunningham's anatomy) mention four drainage areas, quoting the work of Jameson and Dobson (1907). Poirier, Cuneo and Delamere (1913) in "The Lymphatics" (page 199) which is the outstanding book on the lymphatic system, stated "In the stomach there are three distinct lymphatic territories. These territories correspond to the three groups of collecting trunks which we have described." They did not mention the work of Jameson and Dobson.

The literature dealing with the lymphatics at the pylorus may be summarized as follows. All of the observers stated that there is no continuity between the subserous lymphatic system of the stomach and duodenum, except Sappey, who stated that the subserous lymphatics are directly continuous between the stomach and the duodenum and Jameson and Dobson, who found evidence of continuity in one specimen of thirty. All of the outstanding workers in this field (Sappey, Most, Poirier, Cuneo and Delamere, Polya and Navratil, and Jameson and Dobson) stated that the submucous lymphatics of the stomach are directly continuous with those of the duodenum although certain observers (Poirier and Cuneo, Jameson and Dobson) added that these lymphatic vessels are not highly developed.

Material and Methods—The material used in this investigation was obtained from necropsies at the Mayo Clinic. Only normal specimens were used. The youngest subject was a fetus aged 7 months, and the oldest a man aged 66. Most of the specimens were obtained from very young subjects. The stomachs were obtained between one and three hours after death, either injections were made while they were in situ, or the stomach and adjacent organs were removed en masse and injections were then made into the stomach while it was immersed in warm water. The standard apparatus for injection work in the Section on Pathologic Anatomy was used. Constant pressure can be maintained over any period of time.

A modification of Gerota's method was employed. India ink and colored gelatin³⁶ were used as injection mediums. The gelatin mixture, in the liquid state, was essentially of the same consistence as the india ink. It was kept this way by means of a warm water bath. It is an excellent injection medium, for the gelatin hardens when the specimen into which injections are made is placed in a fixative of formaldehyde. Better microscopic sections can be made from such a specimen than from specimens in which india ink alone is used for injection. In all, injections were made into thirty-five specimens. Injections were made into fifteen of these specimens under pressure ranging from 20 to 60 mm of mercury and into twenty specimens under pressure varying from 180 to 460 mm of mercury. The needle was invariably inserted into the submucosa of the stomach and was pushed on until it was between 1.5 and 5 cm from the pyloric sphincter. The injection mass was then allowed to flow into the submucosa. Leakage was not encountered during the time of injection. In ten specimens multiple punctures

36 Gelatin 45 Gm. india ink 60 cc. water sufficient to make 500 cc.

were made in the submucosa, both in the anterior and in the posterior surfaces of the stomach. Injections were made into these specimens under relatively low pressure, from 20 to 60 mm of mercury. Only a small area of lymph vessels was filled from each puncture. By this method injections were made into the entire collecting system of the lymph vessels. In five specimens injections were made into the submucosa of the duodenum with the point of the needle just distal to the pyloric sphincter. Carmine-colored gelatin was the medium used for the duodenal injections. An average of six microscopic sections through the duodeno-pyloric juncture, parallel with the long axis of the pyloric canal, was made from each specimen. A detailed study was made of the lymphatics in this area. The carcinomas of the stomach used in this study were also obtained from the necropsy service at the Mayo Clinic.

Results—In all of the specimens continuity was not evident between the submucous lymphatics of the stomach and the duodenum (figs 8,

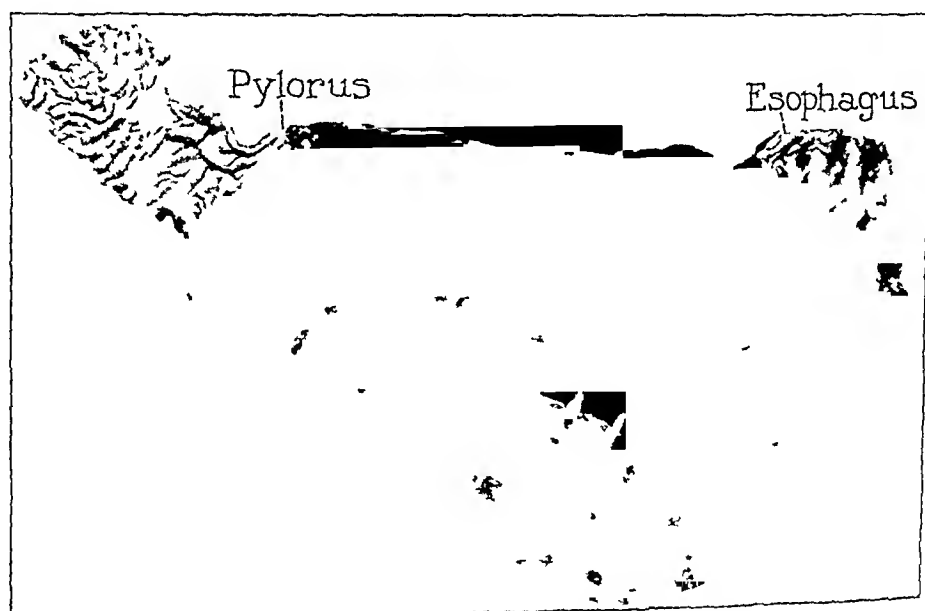


Fig 8—Submucosa of the stomach from a female subject, aged 47 years, into which injections of india ink were made under a pressure of 300 mm of mercury. The needle with which the injection was made is still in place, with the point of the needle in the submucosa 6.5 cm proximal to the pyloric sphincter. The injection mass has been stopped abruptly at the pylorus.

9, 10 and 11). Complete continuity of the lymphatic network was evident in the submucosa of the stomach. A few of the specimens showed direct continuity between the subserous lymphatics of the stomach and duodenum. This was observed only on the posterior aspect of the pylorus. The specimens varied markedly in the ease with which injections were made into the submucosa. In one specimen (fig 12) the injection into the submucosa was easy. With the point of the needle in the submucosa 4 cm proximal to the pyloric sphincter the ink flowed in freely under a pressure of 180 mm of mercury and the entire



Fig 9—Submucosa of the stomach from a male subject, aged 27 years, into which injections of a mixture of india ink and gelatin were made under 20 mm of pressure with the point of the needle in the submucosa, 2.5 cm proximal to the pyloric sphincter. The wall of the stomach is infiltrated with the mass that has been blocked at the pylorus.

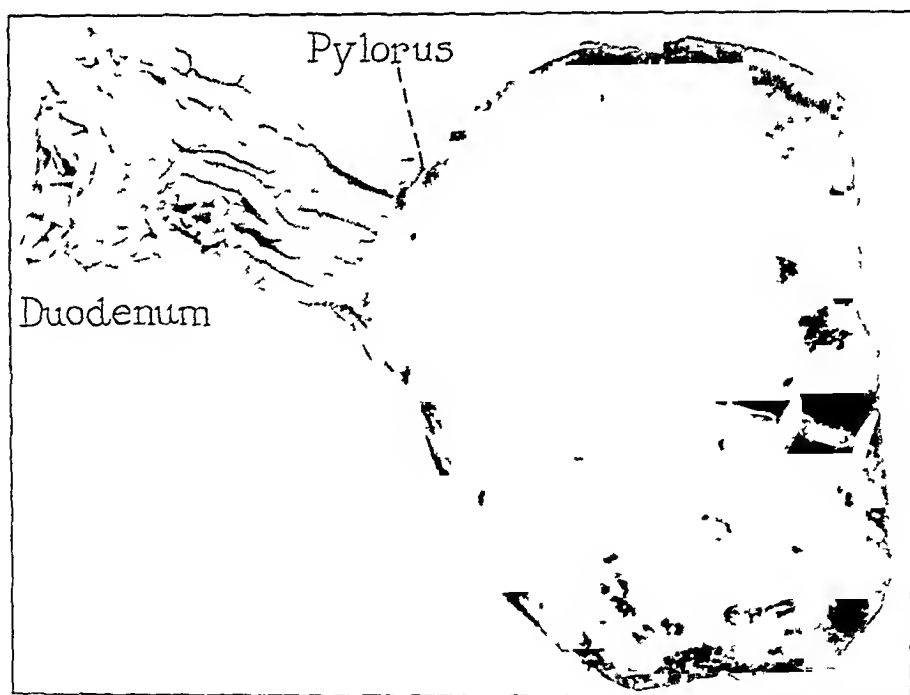


Fig 10—Submucosa of the stomach from a female subject, aged 57 years, into which injections of a mixture of india ink and gelatin were made under 400 mm of pressure, with the point of the needle in the submucosa 3 cm proximal to the pyloric sphincter. The injection mass has been stopped abruptly at the pylorus. The injection was carried out for a period of two and one-half hours.

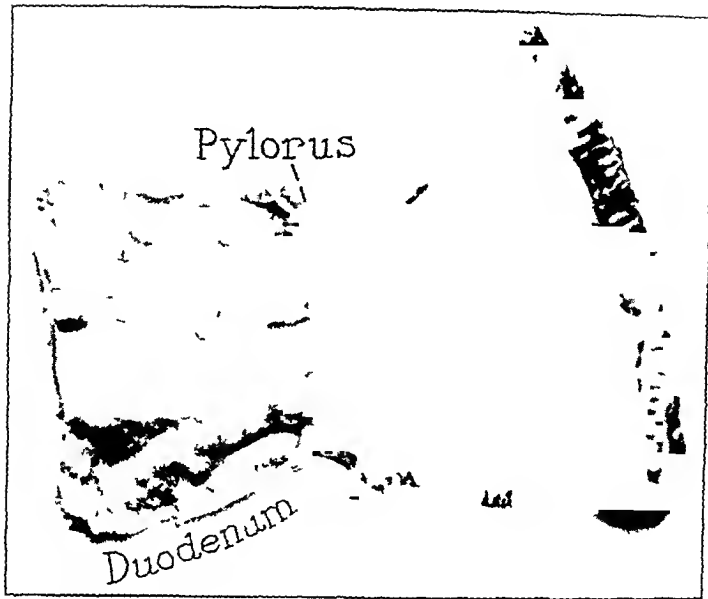


Fig 11—Submucosa of the stomach from a male subject, aged 11 months, into which injections of a mixture of india ink and gelatin were made under 280 mm of pressure, with the point of the needle in the submucosa 2 cm proximal to the pyloric sphincter. This pressure was maintained for thirty minutes after the injection mass reached the pylorus. Only the pars pylorica received the injection as a clamp was applied across the middle third of the stomach. The mass has been blocked at the pylorus.

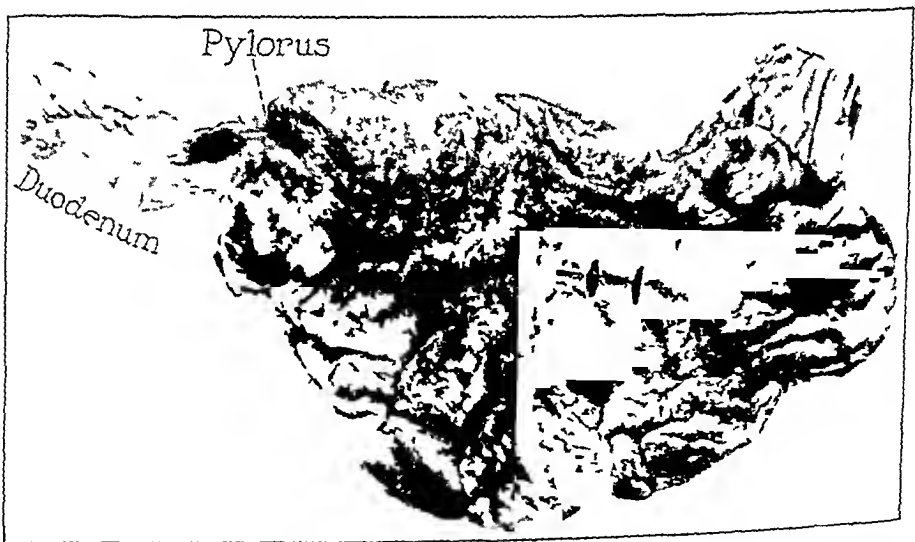


Fig 12—Submucosa of the stomach from a male subject, aged 66 years, into which injections of india ink were made under 180 mm of pressure, with the point of the injection needle in the submucosa 4 cm proximal to the pyloric sphincter. Slight extravasation of ink into the duodenum has taken place.

submucosa was injected within fifteen minutes. After the stomach was well injected, the submucosa at the pyloric sphincter became slowly but markedly distended and remained so for eight minutes, then the ink slowly extravasated into the submucosa of the duodenum, on the posterior aspect, for a distance of 1 cm. In many specimens into which injections were made in exactly the same manner, even under pressure as high as from 300 to 460 mm of mercury, the medium stopped abruptly at the pylorus (figs 8 and 10). After the submucosa at the sphincter had become markedly distended, the pressure was maintained at 460 mm for thirty minutes, or longer, without any extravasation of ink into the duodenum. In one specimen (fig 10) with the point of the needle in the submucosa 3 cm proximal to the pyloric sphincter, after the submucosa had become distended at the pylorus, a clamp was applied across the stomach at its middle portion, proximal to the insertion of the needle, so that the entire pressure of from 420 to 460 mm of mercury was applied to the pylorus for a period of twenty minutes, but there was absolutely no leakage of ink across the pyloric sphincter into the duodenum. A similar procedure was followed with a child's stomach (fig 11) under a pressure of 280 mm of mercury, with similar results. In all of the specimens into which injections were made under high pressure, the stomach was first opened by incision along the anterior surface, midway between the greater and lesser curvatures, the incision extending well down into the duodenum. The state of tonus of the pyloric sphincter was not a factor in these cases, for the pylorus was cut through on the anterior aspect before the injection was started, and the cut margins were either sutured with heavy thread or stomach clamps were applied along the cut margins so as to prevent leakage of the injection medium.

In the majority of specimens it was observed, at the time of injection, that the ink flowed more readily at right angles to the long axis of the stomach. It approached the greater and lesser curvatures, the cardia and the pylorus with decreasing velocity in the order named. In several specimens, by actual measurement, it traveled an average of 12 cm toward the cardia while flowing 2 cm toward the pyloric sphincter, even though the current of the injection mass was directed toward the sphincter. In all of the specimens the injection mass flowed up to the pyloric sphincter and stopped abruptly. In some specimens the submucosa was so distended that it was overhanging the pylorus and projecting into the duodenum, in one specimen the wall of the stomach just proximal to the sphincter was 5 cm thick whereas it was 2 mm thick prior to the injection. Injections were also made into the submucosa of the duodenum in five specimens with the point of the

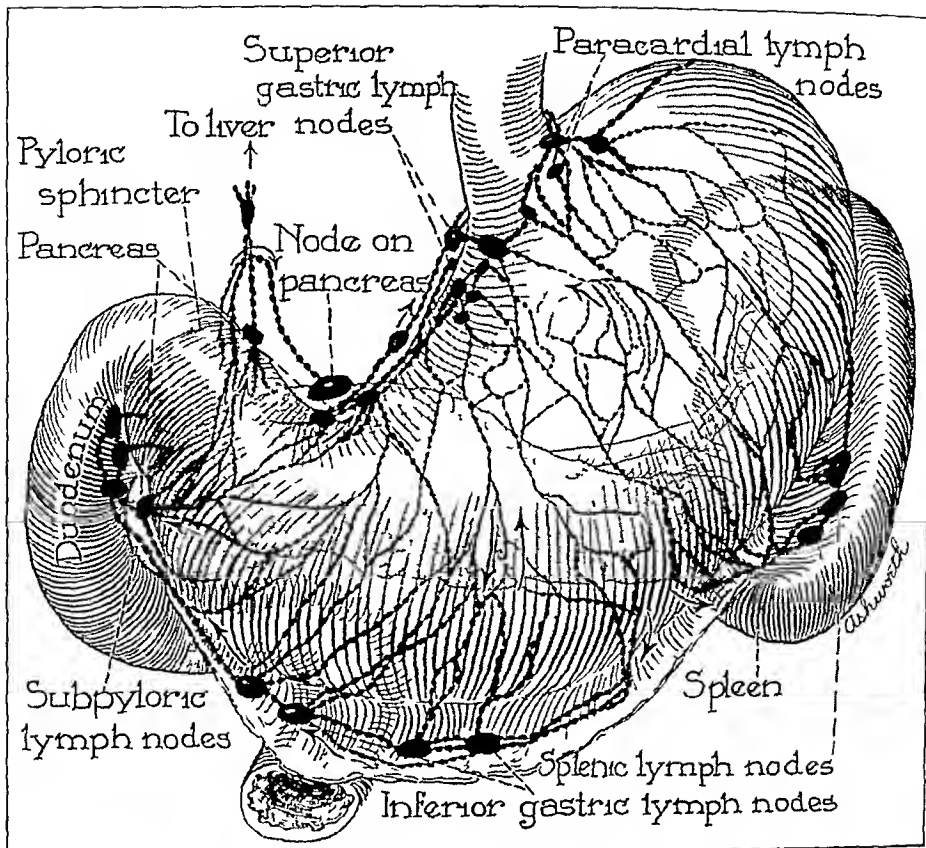


Fig 13—Lymphatic drainage of the stomach (anterior surface), as determined by injections into thirty-five specimens. The arrows indicate the lines of drainage. There are four distinct areas of drainage.

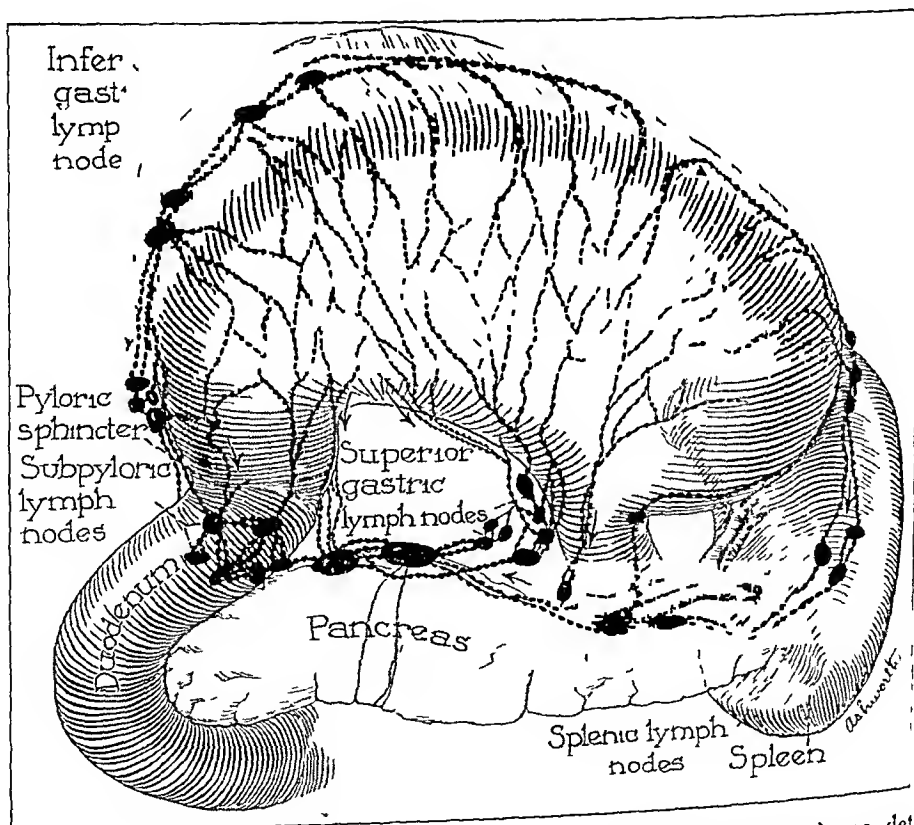


Fig 14—Lymphatic drainage of the stomach (posterior surface), as determined by injections into thirty-five specimens. There are four distinct areas of drainage. The arrows indicate the lines of drainage.

injection needle just distal to the pyloric sphincter. Pressures used here were similar to those used in injections above the sphincter. In each case, the injection medium stopped abruptly at the pylorus.

The lymphatic drainage of the stomach, as determined from these injections, is represented in figures 13 and 14. In figure 13 the drainage is represented by four distinct areas. The largest of these represents the area drained by the lymph nodes along the lesser curvature, and the flow of lymph is toward the cardia. The second most important area is that on the greater curvature, drainage is into the inferior gastric and subpyloric groups of lymph nodes. The third drains toward the splenic group of lymph nodes, and the fourth, which is relatively small, drains the superior distal portion of the pars pylorica to the right suprapancreatic lymph nodes above the upper border of the pancreas. The collecting vessels from the fourth group may also drain into the biliary lymph nodes. In two specimens a direct communication between the pylorus and the so-called sentinel node at the hilus of the liver was observed. On the anterior surface of the gastrohepatic omentum were two or three small lymph channels which extended from the pylorus to a lymph node at the hilus of the liver. The drainage of the posterior surface of the stomach, represented in figure 14, corresponds with the areas described for the anterior surface. However, the boundaries of these areas of drainage must not be defined too accurately, for, if the normal drainage in a given direction is blocked, the injection medium readily flows in the opposite direction.

It should be emphasized that lymph vessels that seem to enter the lymph nodes are frequently only in contact with them on their way to more distant lymph nodes. This was repeatedly observed while the injections were being made into the specimen. The lymph node nearest the site of the initial injection was not necessarily the first node to be filled with the injection mass, the more distal nodes were frequently filled first. This was observed repeatedly along the lesser curvature of the stomach, and in other areas. In figure 15, the variations in the submucous lymphatic drainage at the pylorus are represented. The injection medium passes through the muscular layers of the pars pylorica either just proximal to the sphincter or, in rare instances just distal to it, and then continues on the peritoneal surface of the duodenum toward the subpyloric lymph nodes, to the nodes above the upper border of the pancreas or in rare instances to the biliary lymph nodes. In one specimen (fig 15*b*) an indirect communication between the lymphatics of the submucosa of the stomach and those of the duodenum was demonstrated. This indirect communication undoubtedly accounts for the fact that in cases of carcinoma arising in the pyloric canal, near the sphincter carcinomatous ulcers may be found both proximal and distal

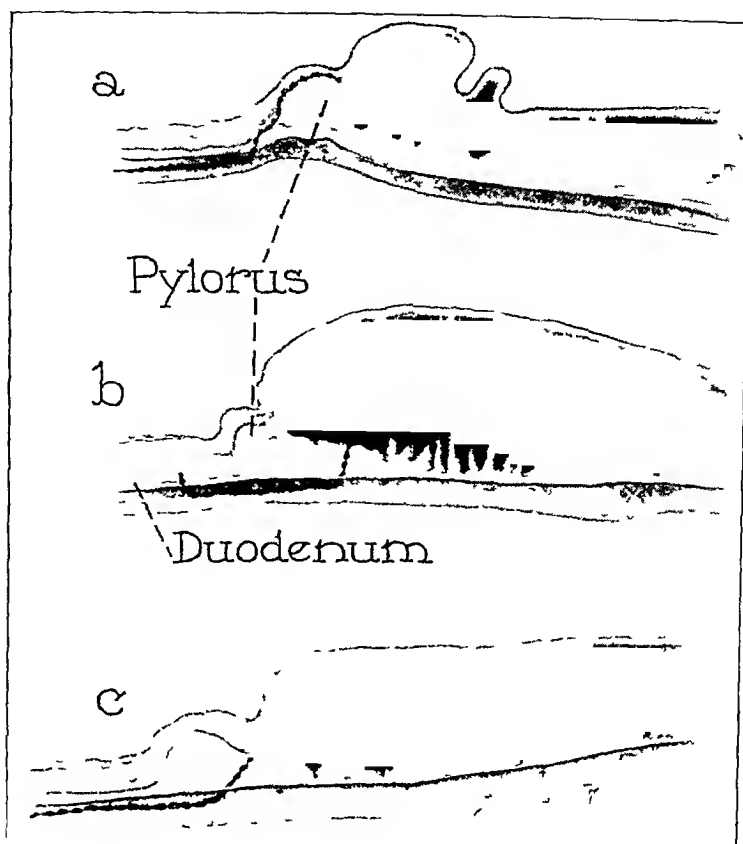


Fig 15—Lymphatic drainage at the pylorus, showing variations in the sub mucous drainage in this area

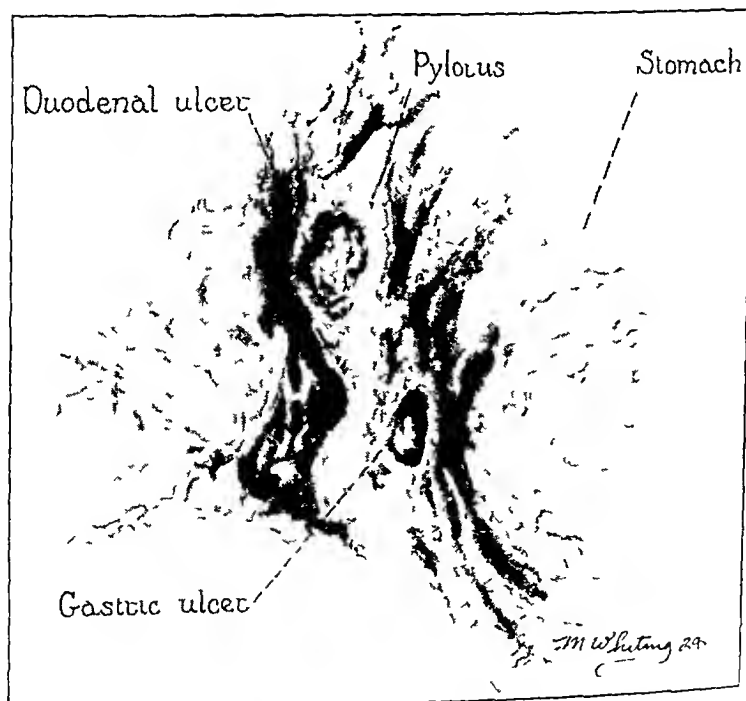


Fig 16—Carcinoma of the stomach. There are carcinomatous ulcers both proximal and distal to the pylorus, but the pyloric mucosa is still intact (After Nagel)

to the pyloric sphincter (fig 16) with normal intact mucosa between the two ulcers Nagel³⁷ reported a case in 1925 I made serial sections through the specimen and demonstrated that the two carcinomatous ulcers were connected by a relatively broad chain of carcinoma cells along the lymphatic channel, as indicated in the indirect communication between the submucosa of the stomach and that of the duodenum

Comment—There can be no question but that there is a discontinuity between the submucous lymphatics of the stomach and those of the duodenum This is explained by the presence of a connective tissue septum at the pylorus (fig 17) which not only separates the submucosa

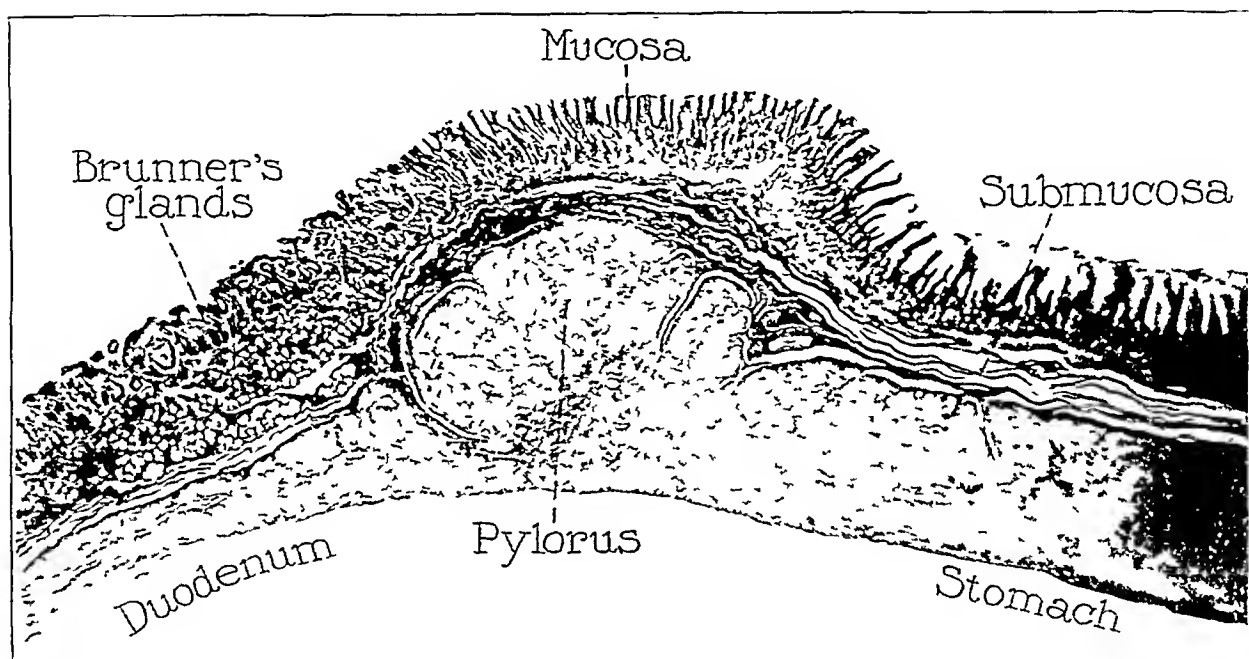


Fig 17—Longitudinal section through the posterior surface of the pylorus The pyloric sphincter is well outlined, and a break in the circular musculature is seen distal to the pylorus The subject was a boy, aged 6 months (Reduced from $\times 18$)

of the stomach and duodenum, but also separates the circular musculature of the stomach from the corresponding circular coat in the duodenum Thus at the pylorus there is a double barrier to the spread of carcinoma which is represented by the connective tissue septums and the discontinuity of the submucous lymphatics This undoubtedly explains why carcinoma of the stomach, regardless of how extensive it may be, practically always stops at the pylorus and rarely, if ever, invades the duodenum (figs 18 to 21) When extension in that direc-

³⁷ Nagel, G W Unusual Conditions in the Duodenum and Their Significance Arch Surg **11** 529 (Oct) 1925

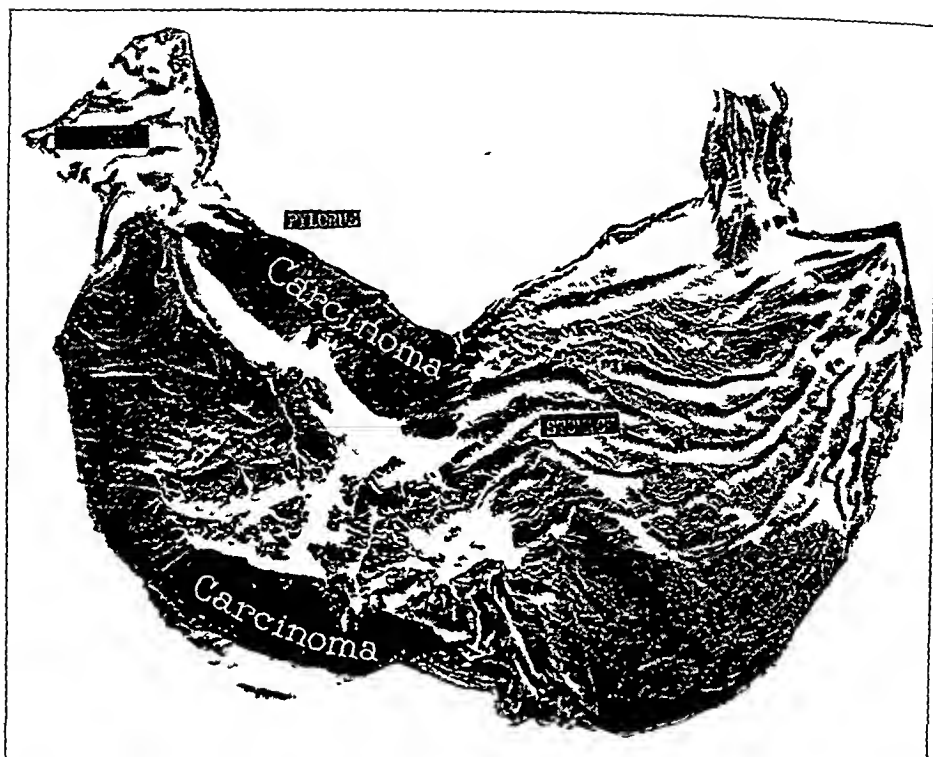


Fig 18—Annular carcinoma of the pyloric portion of the stomach. The growth extends up to the pylorus, where it stops abruptly. The duodenum was not involved. The specimen is from a male subject, aged 44 years.

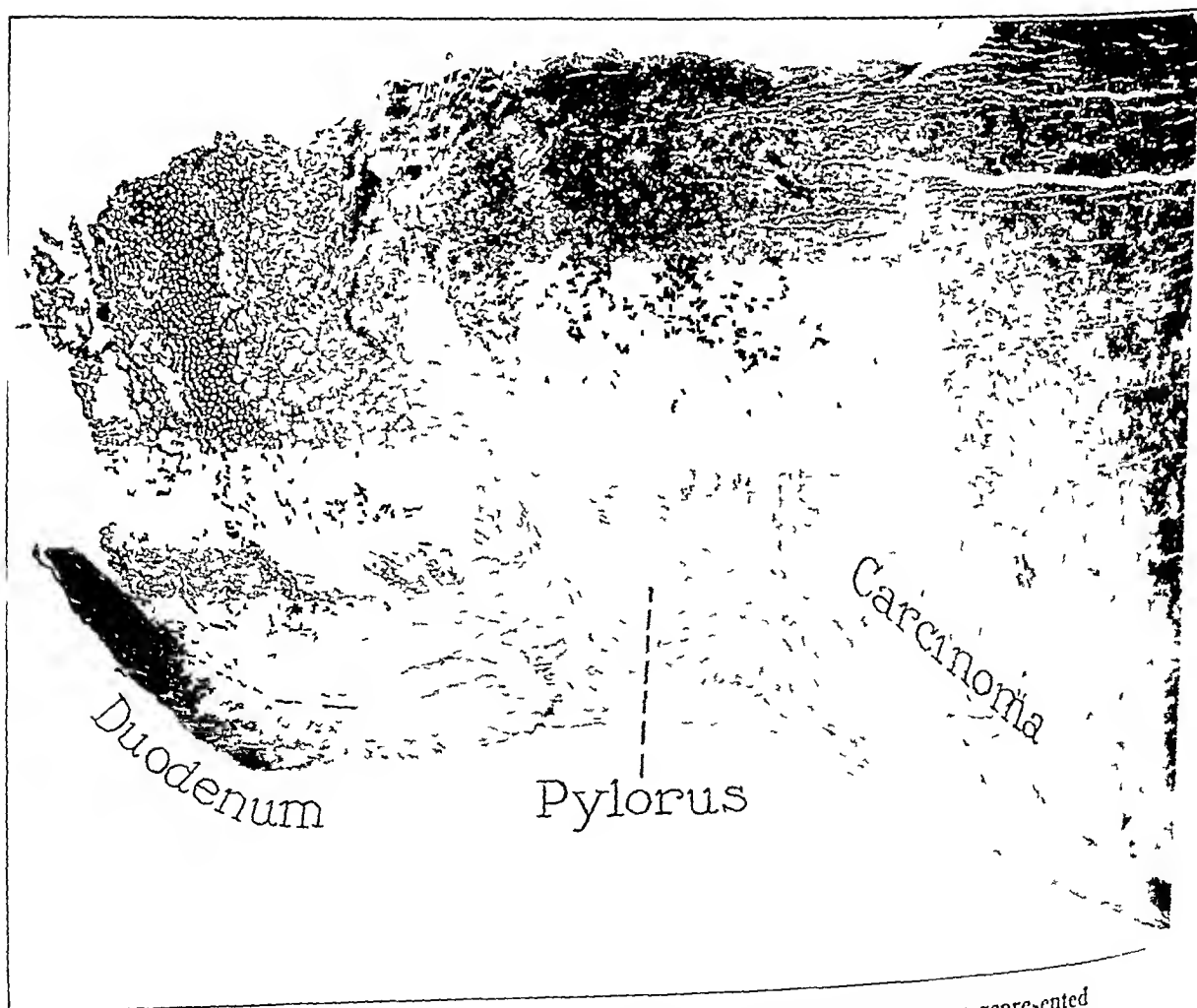


Fig 19—Longitudinal section through the pylorus of the specimen represented in figure 18. The pyloric sphincter is still intact, and the carcinoma stops abruptly at the sphincter.

tion does occur, it is usually along the peritoneal aspect of the duodenum, as indicated in figures 20 and 21. In figure 21, the carcinoma has extended along the submucosa of the stomach, up to the pylorus, and then through the muscle wall, and along the outside of the duodenum, thus following the lymphatic drainage as indicated in figure 15c. This line of drainage has been the usual one observed in all of the carcinomas studied, which includes a series of more than 200 cases. It should be remembered, however, that no barrier in the human body can hold out indefinitely against the invasion of carcinoma, and if the patient with an extensive carcinoma of the pars pylorica should live long enough, I feel sure that the duodenum eventually would be freely invaded. Of all the tissues in the body, connective tissue apparently offers the best resistance to the spread of carcinoma.

The ease with which the gelatin mass could be injected into the submucosa, in certain specimens, and the difficulties encountered in others are of marked interest, in view of the spread of carcinoma along this route. The variations in the density of the normal connective tissue in the region probably account for the fact that in some small carcinomas of the stomach there is extensive involvement of the adjacent lymph nodes, while in other cases in which relatively large carcinomas are present, there is little, if any, spread to the regional lymph nodes, even when the grade of malignancy, as determined by Broders' classification, is the same. Bothe³⁸ showed from a study of 100 cases that the size of the carcinoma bears no definite relation to the involvement of the regional lymph nodes. The largest growth he studied measured 14 by 11 cm., and the smallest, 2 by 1 cm. In spite of the difference in the size of these specimens, the smaller one showed involvement of all of the lymph nodes that were found with the specimen, whereas with the larger specimen only five of the fifteen nodes found were affected. These were resected specimens. This is in accord with the study of 200 cases previously made by MacCarty and Blackford.³⁹

It should be remembered that nearly a third of all carcinomas occur in the stomach, and of these, 80 per cent are found in the pars pylorica (W. J. Mayo⁴⁰). For this reason, exact knowledge of the lymphatic drainage of the stomach is of great practical importance. The curability of carcinoma depends largely on whether or not the lymph nodes are involved. Balfour and Hargis⁴¹ recently showed that when the lymph

38 Bothe, F. A. Lymphatic Involvement in Cases of Carcinoma of the Pyloric End of the Stomach, *Surg. Gynec. Obst.* **44** 761 (June) 1927.

39 MacCarty, W. C., and Blackford, J. M. Involvement of Regional Lymphatic Glands in Carcinoma of the Stomach, *Ann. Surg.* **55** 811 (June) 1912.

40 Mayo, W. J. Cancer of the Stomach. Its Surgical Treatment, *Surg. Gynec. Obst.* **14** 115 (Feb.) 1912.

41 Balfour, D. C., and Hargis, E. H. Cancer of the Stomach, *Am. J. M. Sc.* **173** 773 (June) 1927.

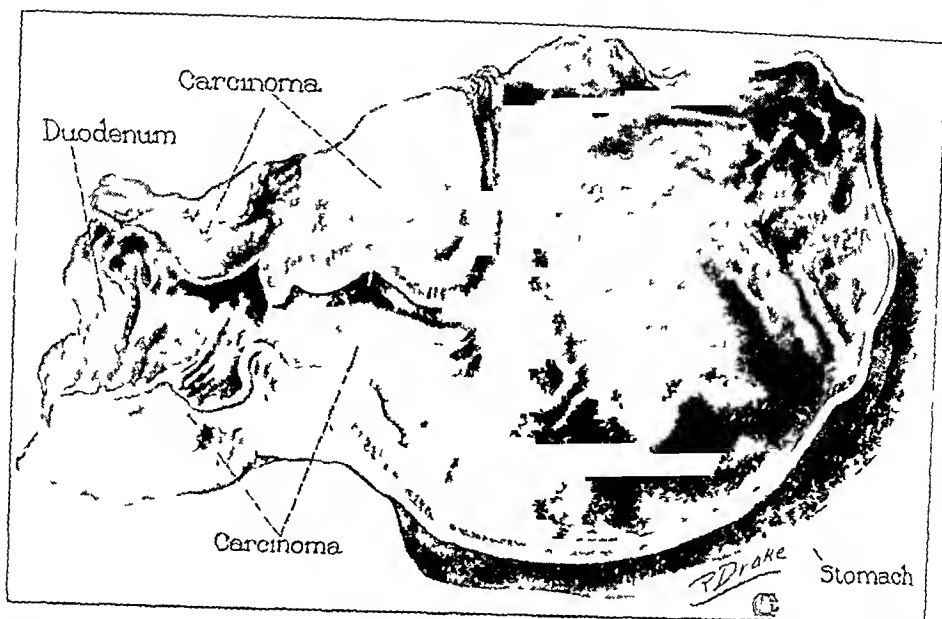


Fig 20—Carcinoma of the stomach The growth extends to the peritoneal surface of the pars pylorica and duodenum The duodenal mucosa is not involved The specimen is from a male subject, aged 37 years

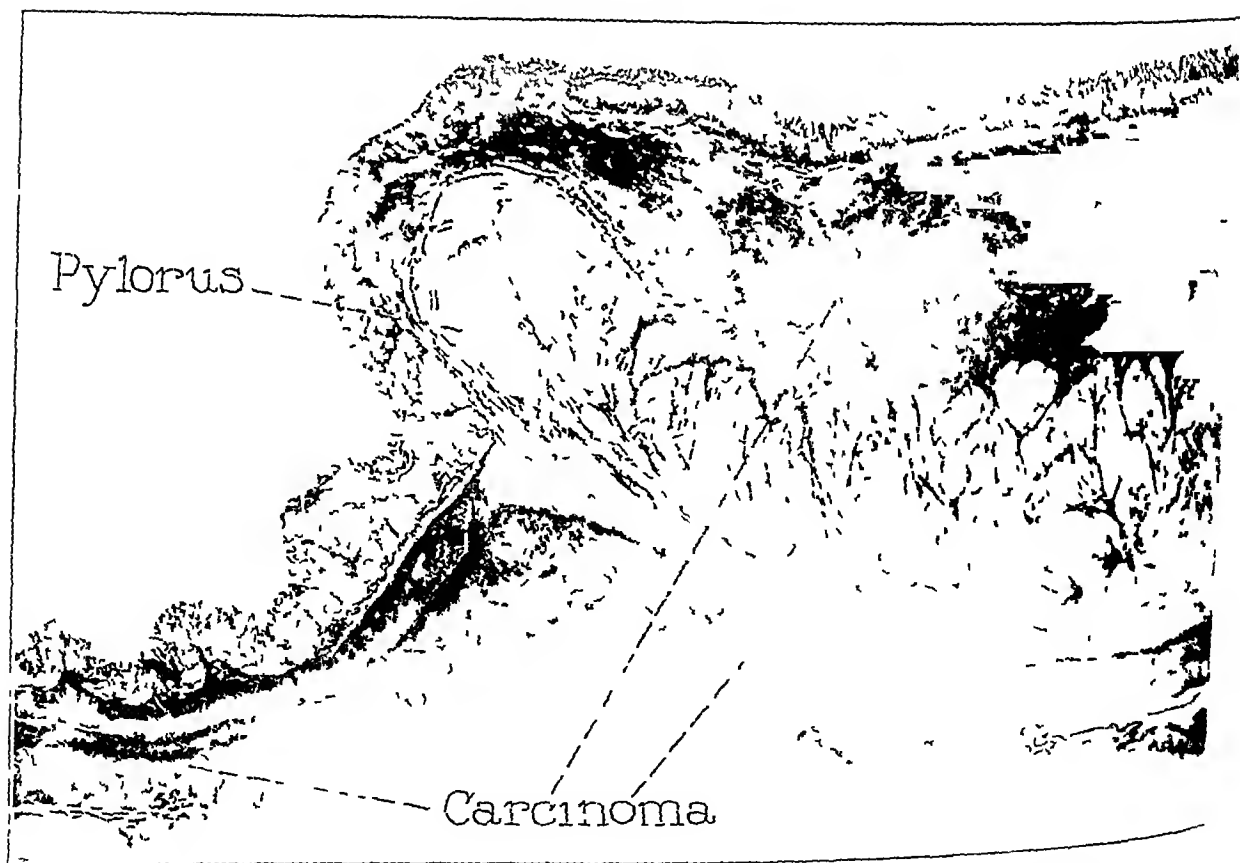


Fig 21—Longitudinal section through the pylorus of the specimen represented in figure 20 The submucosa of the stomach is distended with the infiltrating carcinoma which extends to the outside of the pars pylorica and duodenum The duodenal mucosa is not involved

nodes were not involved, 52 per cent of the patients were alive and well at the end of three years, whereas, when the lymph nodes were involved, only 19 per cent were alive and well at the end of three years. Another point worthy of emphasis is that in ordinary injections of the lymphatics of the stomach, it was observed that lymph vessels that seemed to enter lymph nodes were frequently only in contact with them on their way to more distant lymph nodes. This fact may explain why, in cases of carcinoma of the stomach, the surgeon often finds that the disease has missed the adjacent lymph nodes and has involved distant nodes. Resection for carcinoma should never be undertaken without careful exploration of the distant lymph nodes.

The possibility of the spread of carcinoma along the lymphatic channels which run with the pyloric artery should be emphasized. Studies at the Mayo Clinic (MacCarty and Blackford and Bothe) did not include this group, and Jamieson and Dobson were unable to find any reference in the literature to such a study. These lymphatic vessels drain a well marked region of the pylorus and are usually four or five in number. I have recently demonstrated this region of drainage in anesthetized dogs, by injection of india ink into the stomach, and it seems to be relatively larger in dogs than in man. The channels drain directly into the lymph nodes lying along the upper border of the pancreas. Frequently, one of these lymphatic vessels runs down the posterior surface of the duodenum to join the biliary lymphatic system. These vessels are not easy to remove in ordinary resections of the stomach. The possibility of a direct communication between the distal portion of the pylorus and the nodes at the hilus of the liver should be remembered, even though it was observed in only two of thirty-five specimens. There were two or three small lymph channels on the anterior surface of the gastrohepatic omentum, extending from the pylorus to the lymph node at the hilus of the liver. The usual procedure, therefore, in radical operations for carcinoma of the pyloric portion of the stomach can never give the surgeon absolute assurance that he has removed all of the first lymphatic relays.

SUMMARY

The continuity of the myenteric plexus from the stomach to the duodenum has been demonstrated by reconstruction models, and the possible significance of these data has been considered.

An investigation was undertaken to determine the lymphatic drainage of the stomach and the relationship between the lymphatics of the stomach and those of the duodenum. India ink and india ink and gelatin mixtures were injected into thirty-five specimens. In none of the specimens was there any demonstrable continuity between the submucous

lymphatics of the stomach and those of the duodenum. An indirect communication between the submucous lymphatics of the stomach and those of the duodenum has been demonstrated. In two specimens there was a direct communication between the pylorus and a lymph node at the hilus of the liver. The drainage of the stomach is represented by four distinct areas, the largest of which represents the area drained by lymph nodes along the lesser curvature, the second most important is that on the greater curvature which drains into the inferior gastric and subpyloric groups of lymph nodes. The third drains toward the splenic group of nodes, and the fourth drains the distal portion of the pars pylorica to the nodes above the pancreas.

ATTITUDES ASSOCIATED WITH LESIONS ABOUT THE HIP JOINT

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One may frequently gain considerable information from a careful study of the position of deformity or attitude of the lower extremities associated with lesions involving the hip joint. A characteristic gait not infrequently enables one to suspect a certain lesion, and it is not uncommon for one to suspect a definite lesion of the hip joint from careful inspection alone without resorting to further examination by palpation, manipulation, measurements, muscle tests, roentgen and laboratory tests, since certain lesions about the hip joint are manifested by more or less characteristic attitudes. The purpose of this paper is not to point out that the observation of the position of deformity or attitude of the lower extremities will make possible a "snap" diagnosis, but to emphasize the fact that such an observation may aid in the differential diagnosis and in determining further examination necessary to arrive at a correct opinion. The internist may be encouraged to resort to special tests after the observation of a characteristic blood picture, or the ophthalmologist may be directed along a definite course of investigation after noting certain alterations in the fundus. Although a gait, a blood picture, a change in the fundus or an attitude may be a fairly constant manifestation of a certain lesion, it does not justify disregard of the fundamental teaching that before instituting treatment a positive diagnosis should be established when possible by a complete examination exhausting all necessary clinical and laboratory tests.

The particular attitude or position of deformity of the lower extremities should be recognized during the first part of the examination, the period of inspection. It is important to understand certain fundamental principles involved in the examination of the lower extremities. Before one can state definitely the position of the extremities, it is essential to determine the position of the pelvis and the lumbar spine. For instance, a patient may appear to lie in bed with an extremity held in abduction, but careful examination will demonstrate that the hip is actually in a position of adduction (figs 1 *A* and *B*). The apparent abduction is the result of a tilting or rotation of the pelvis on its anteroposterior axis. In the same way, rotation of the pelvis on its vertical axis may

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Fig 1—In *A*, the attitude of the left lower extremity appears to be abduction and external rotation. Actually, the extremity is in a position of adduction and external rotation which is determined only when the pelvis is placed on a transverse and horizontal plane (see fig 1 *B*). In *B* the same patient is seen as in figure 1 *A*, with the pelvis on a transverse and horizontal plane revealing the correct attitude of adduction and external rotation.

result in a faulty interpretation of the degree of internal or external rotation of an extremity. A correct interpretation of the position of deformity of an extremity can be made only when the pelvis is placed on a transverse and horizontal plane without rotation on either its vertical or horizontal axis. The presence of a flexion deformity of the hip joint cannot be determined by inspection of the involved extremity alone, since it may be masked by the development of a compensatory lumbar lordosis (figs 2 *A* and *B*). It is best to examine a patient on a

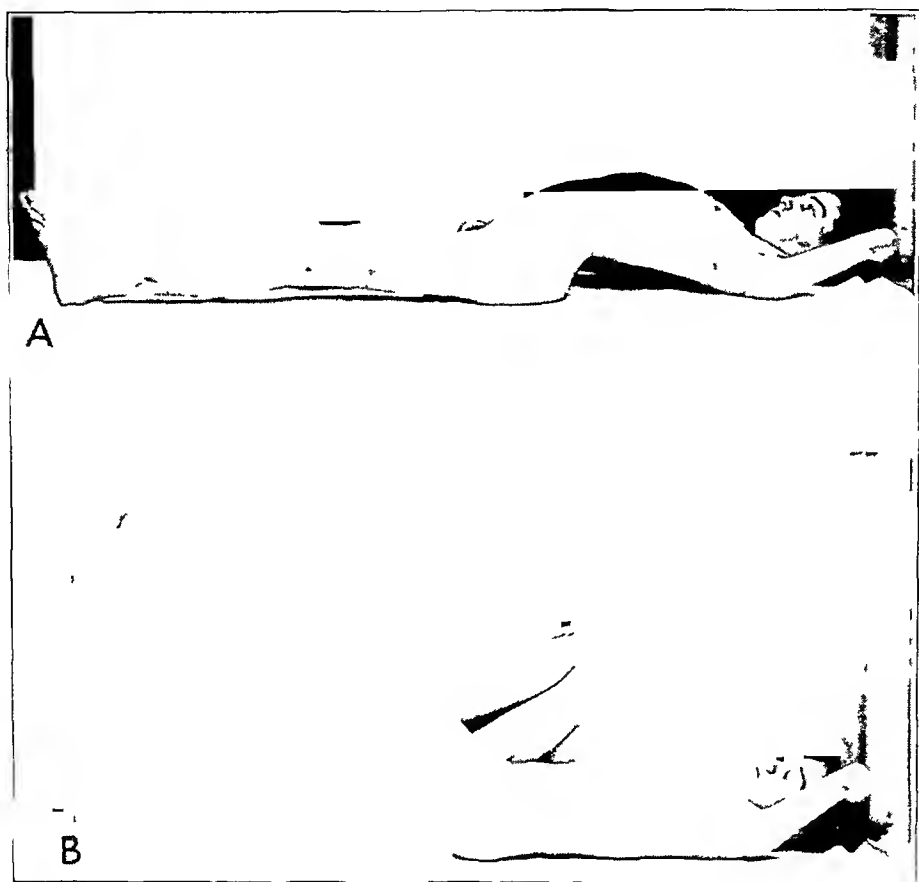


Fig 2—In *A*, the 45 degree flexion deformity of the hip is not apparent because of the presence of a compensatory lumbar lordosis. In *B*, obliteration of the lumbar lordosis by approximating the right knee to the chest makes the flexion deformity of the left hip apparent.

firm mattress or examining table in order to have the pelvis and lumbar spine under control.

The position of deformity assumed by the involved extremity depends upon many factors, namely muscle spasm, muscle paralyses, muscular incoordination, disturbed muscle balance and mechanical alterations following trauma, joint distention, simple joint irritation, joint destruction, gravity, pain and instinctive efforts of the patient to gain comfort.

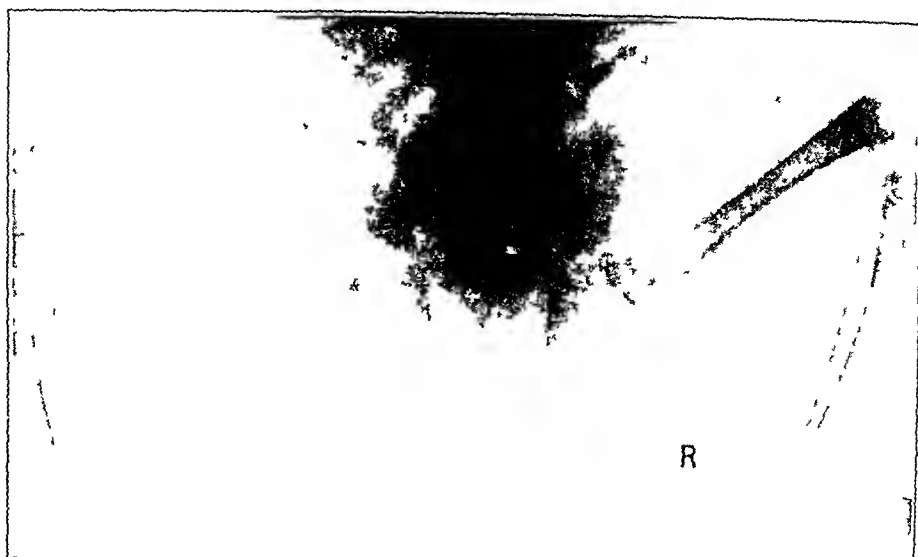


Fig 3—"Frog attitude" assumed during the acute stage of infantile scurvy. Note the subperiosteal hemorrhage over the lower portion of the right tibia and the epiphyseal halos (See fig 4)

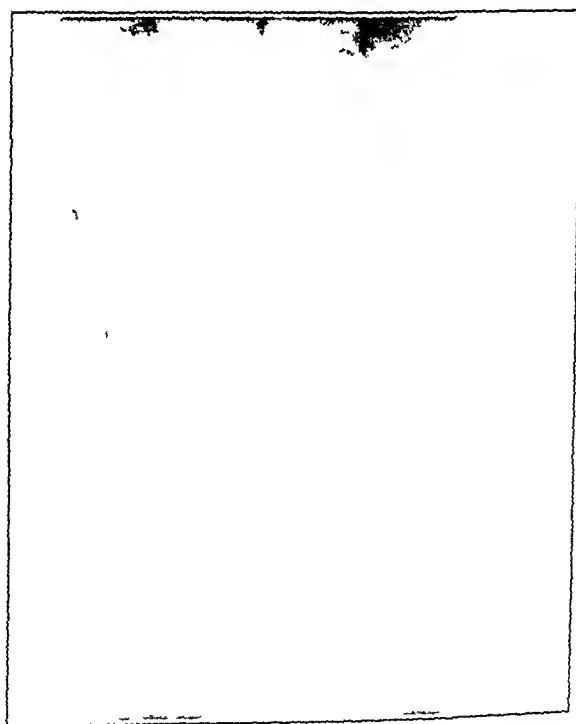


Fig 4—Functional position of the lower extremities following correction of the frog attitude. Note calcification of the massive subperiosteal hemorrhage encircling the shaft of the right femur

The attitude may be the result of one or of a combination of several of the foregoing factors, and it may change during the course of a disease if one factor gradually assumes a more important rôle, replacing the effect of another. For instance, a position of comfort in abduction may be replaced by the position of adduction following the development of muscle spasm.

A classification of lesions about the hip joint that present fairly constant attitudes may be outlined according to age periods, since certain diseases affecting the hip joint manifest their clinical onset during definite age periods (see table). The pseudoparalyses of rickets, scurvy

Attitudes Associated with Hip Joint Lesions

Age Period of Infancy	Age Period of Childhood	Age Period of Adolescence
Pseudoparalyses of	(a) Tuberculosis of hip joint	Separation of upper femoral epiphysis
Rickets	Flexion {	Adduction and external rotation
Scurvy		
Syphilitic epiphysitis		
Frog attitude	(b) Spontaneous dislocation of hip joint	
	Flexion, adduction, internal rotation	
	(c) Acute septic arthritis of hip joint	
	Flexion {	
	(d) Chronic deforming arthritis (Still's disease)	
	Flexion (adduction, internal rotation)	
Age Period of Early Adult Life		Age Period of Late Adult Life
(a) Spondylitis deformans (Rhizomelic)		(a) Malum coxae senilis
(Bent ankylosed position)		Flexion, adduction, external rotation
Flexion, adduction of hips		(b) Fracture of neck of femur
Flexion or extension of spine		Adduction, external rotation
(b) Traumatic dislocation of hip joint		
Anterior dislocation—		
Flexion, abduction, external rotation		
Posterior dislocation—		
Flexion, adduction, internal rotation		

and syphilitic epiphysitis are observed during the period of infancy. Septic arthritis of the hip, primary or secondary to a remote infection, may appear at any age, but is most common during the periods of childhood and adolescence. The chronic deforming arthritides that present quite constant attitudes of the lower extremities are Still's disease and spondylitis rhizomelica, which have their onset of symptoms during the periods of childhood and early adult life, respectively. The greater number of cases of tuberculosis of the hip begin during the period of childhood, although they may appear at any age. Spontaneous dislocation of the hip joint may occur during any age period, but the majority of cases develop during the period of childhood. Epiphyseal

coxa vara, or separation of the upper femoral epiphysis, invariably begins during the period of adolescence. The onset of symptoms in most cases is at about the age of 14 years. Traumatic dislocation of the hip joint is most frequently seen during early adult life, when exposure to severe trauma is more common. "Malum coxae senilis," or chronic hypertrophic arthritis localized to the hip joint, is, as the name implies, a disease of late adult life. Fracture of the femoral neck is usually an injury of old age, though it may occur at any time.



Fig 5—This attitude resulted from the development of contractures about either hip as the patient lay in the frog attitude during the acute stage of rickets. Functional position of the hips was readily obtained by skin traction. Note the flaring of the femoral shafts at the epiphyseal disk regions and the increased density of the femoral shafts on the concave sides.

I have observed four children who were admitted to the clinic with the lower extremities in the typical "frog" position (flexion 90 degrees, abduction 90 degrees and external rotation 90 degrees). Clinical and roentgen examination demonstrated evidence of active rickets in two cases and early infantile scurvy with subperiosteal hemorrhages in one.

case (figs 3 and 4) The lower extremities of three of these children were tender on palpation and painful on manipulation, clinically manifested by pseudoparalyses The fourth child was admitted to the clinic with the lower extremities fixed in the "frog" attitude as a result of contractures about the hips (fig 5) Examination showed evidence of healed rickets, and it was assumed that the child lay in the "frog" position during the active tender stage of rickets with subsequent development of contractures resulting in a fixed deformity Adhesive traction was applied to the lower extremities over a period of several



Fig 6—Flexion, abduction and external rotation attitude assumed during the early stage of tuberculosis of the right hip joint with an insidious onset

weeks, and complete correction was gradually obtained This case clearly demonstrated the importance of early correction of the "frog" attitude during the stage associated with pseudoparalyses to prevent the development of a fixed deformity This is easily accomplished by proper adjustment of pillows or sand bags or adhesive skin traction maintaining the lower extremities in the optimum position for return of function

Congenital syphilis may be manifested as an acute syphilitic epiphysitis of the hips associated with pseudoparalyses—the pseudoparalyses of Parrot The lesion occurs along the line of ossification in long bones

and resembles the epiphyseal disturbance of rickets. Undoubtedly the "frog" attitude may be assumed during the acute and tender stage of this disease when associated with pseudoparalyses. I have never observed this lesion. In general, the observation of the "frog" attitude during the age period of infancy should suggest rickets, scurvy or acute syphilitic epiphysitis with pseudoparalyses.

Malposition is one of the most common evidences of tuberculosis of the hip joint. The attitude of the involved extremity varies according to the stage of the disease and whether the onset is insidious or acute. When the onset is insidious, the malposition usually observed during the early stage when there are symptoms of simple irritation of the



Fig 7—This photograph may illustrate either instinctive traction applied to the left lower extremity or a method used by the patient to immobilize the right lower extremity. (Patient with tuberculosis of the right hip joint.)

joint with effusion is flexion, abduction and external rotation (figs 6 and 7). Late in the disease when there is definite involvement of the cartilage and destruction of the joint the malposition, as a rule, is flexion, adduction and internal rotation (figs 8, 9 and 10). The acute tuberculous hip is held in flexion, associated with either abduction and external rotation or adduction and internal rotation. The flexion deformity is a constant malposition, abduction is always associated with external rotation and adduction with internal rotation. The factors that determine the malposition in an individual case cannot be satisfactorily determined.

Spontaneous or pathologic dislocation of the hip joint more commonly observed during early life, presents a fairly constant malposition of the involved extremity in flexion, adduction and internal rotation. The position is one of instability and is productive of dislocation (figs 11 and 12). The mechanism of production of spontaneous dislocation is a derangement of the normal action of the muscles surrounding the hip joint and is not dependent on destruction of bone or ligament. The normal muscular arrangement about the hip joint may be altered by muscle spasm, which is always present during the acute stage of infection of the hip joint, flaccid paralysis of anterior poliomyelitis and

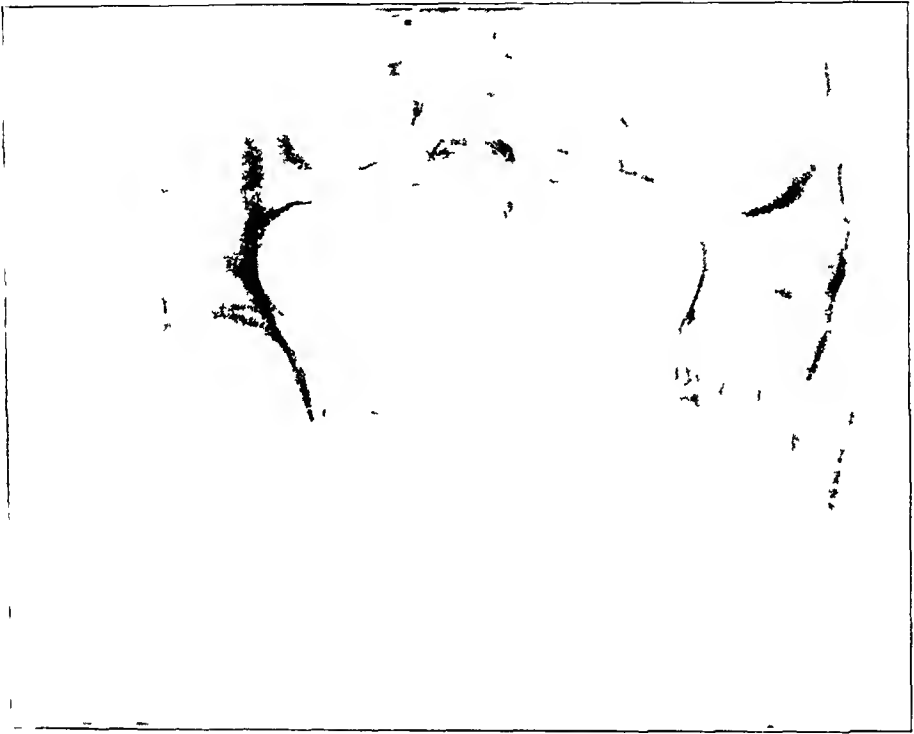


Fig 8—Flexion, adduction and internal rotation attitude associated with late tuberculosis of the left hip joint with complete destruction of the femoral head and the formation of a wandering acetabulum

muscle incoordination in spastic paralysis. This attitude is a dangerous one and should be recognized early and corrected before the occurrence of the dislocation. The attitude is easily overlooked early in the disease unless the position of the pelvis and lumbar spine are carefully studied. The patient may lie in bed with the legs parallel, however, one extremity may be in marked adduction with the pelvis rotated on its anteroposterior axis, and if unrecognized a faulty interpretation of the attitude is made. Also the flexion deformity may not be apparent because of the development of a compensatory lumbar lordosis. Early recognition of

"the position of instability" should be emphasized because of the frequent resulting spontaneous dislocation of the hip which is preventable but when once established is corrected with much difficulty. It is a fundamental principle that a patient with an acute infection of the hip



Fig 9—Late tuberculosis of the hip. The flexion deformity is masked by a compensatory lumbar lordosis.

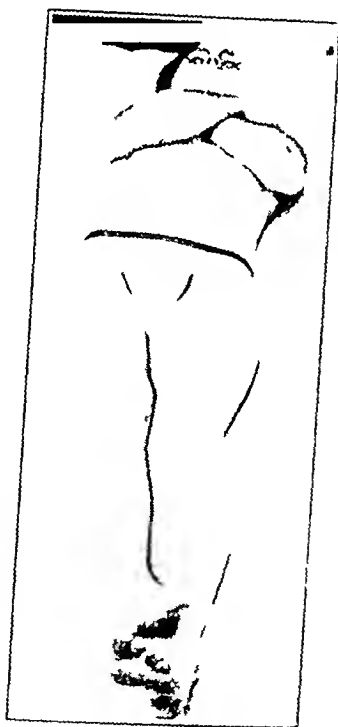


Fig 10—Same as figure 9

joint should be properly arranged in bed either on a firm mattress or on a Biadroid frame so as to have the pelvis and lumbar spine under control. The pelvis should be on a transverse and horizontal plane and the lumbar spine flat. It is often useful to mark the skin with an ink line or to place a colored adhesive tape between the two anterior superior



Fig 11—Purulent hip joint in position of stability flexion and abduction Note the pathologic, epiphyseal separation with slight displacement



Fig 12—Same case as in figure 11 one day later, with hip joint in "position of instability" flexion and adduction resulting in spontaneous dislocation



Fig 13—Attitude of flexion, abduction and external rotation associated with septic arthritis of the right hip joint

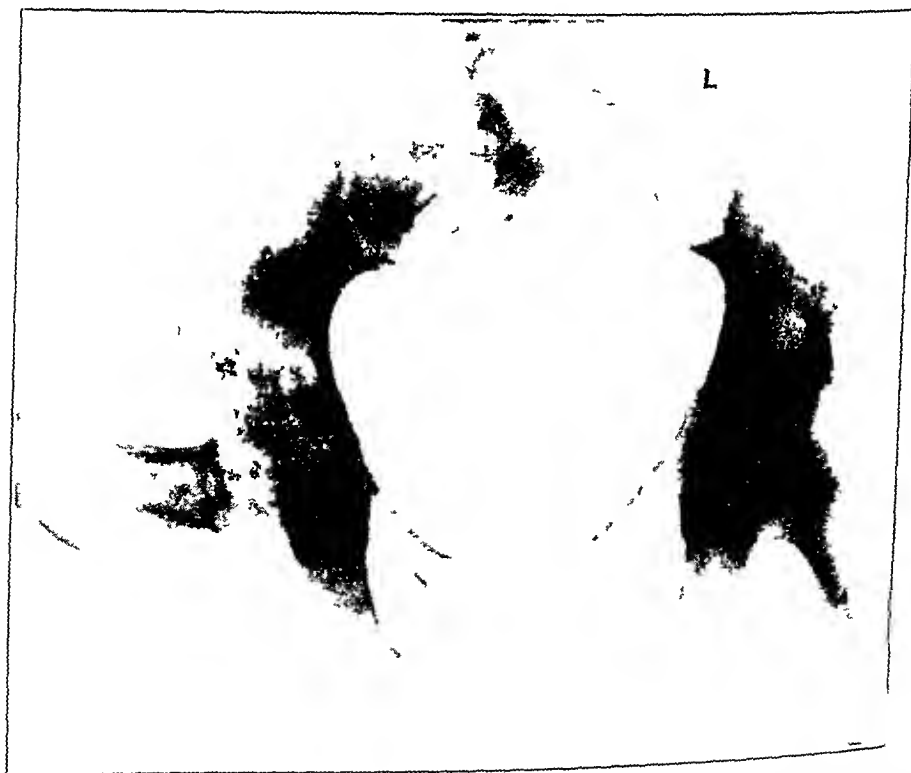


Fig 14—Roentgenogram of patient in figure 13, demonstrating the attitude of flexion, abduction and external rotation associated with septic arthritis of the right hip joint



Fig 15—Chronic deforming arthritis or Still's disease with flexion deformities of the hip joints. Note the flexion, adduction and internal rotation attitude or "position of instability" of the left lower extremity with resulting spontaneous dislocation of the left hip

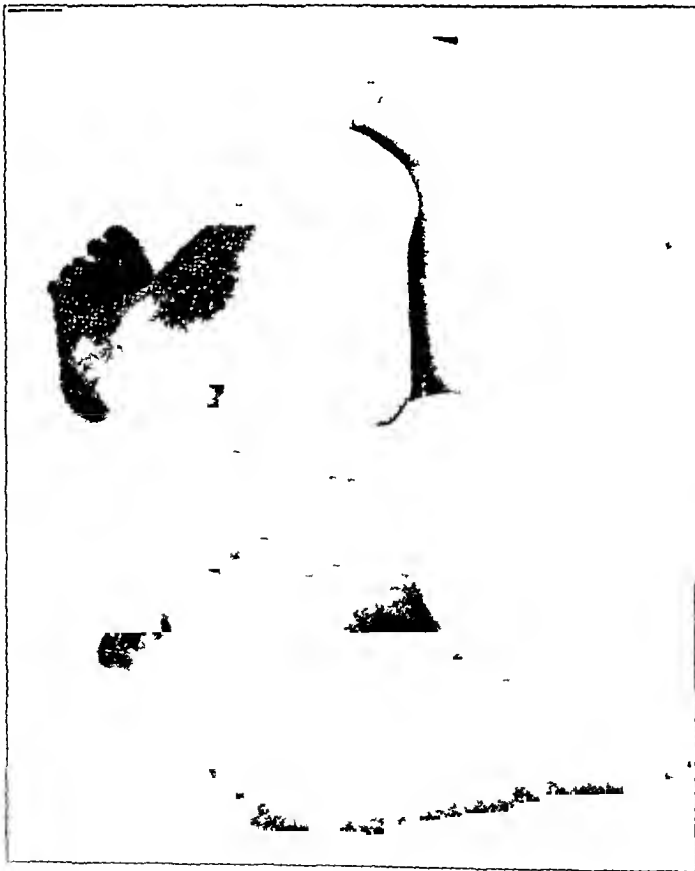


Fig 16—Same as figure 15



Fig 17

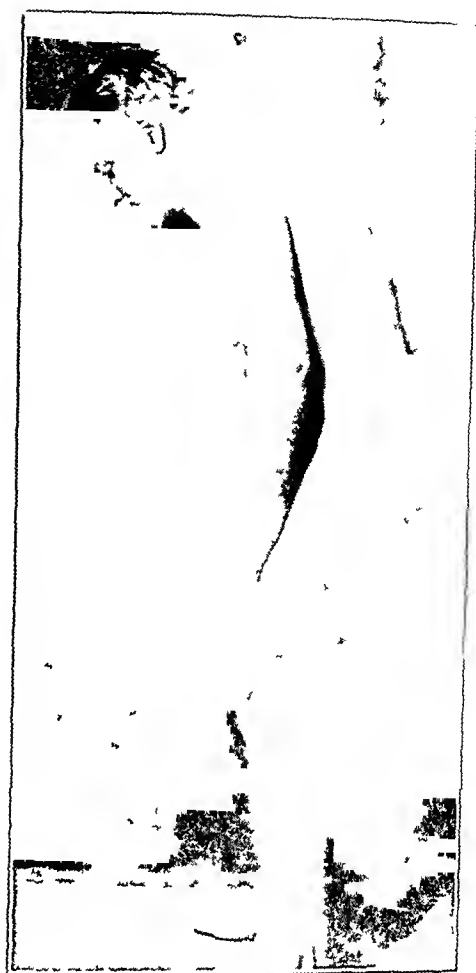


Fig 18

Fig 17 —Bent ankylosed attitude in spondylitis rhizomelica or ankylosing arthritis of the spine and hip joints

Fig 18—Same as figure 17

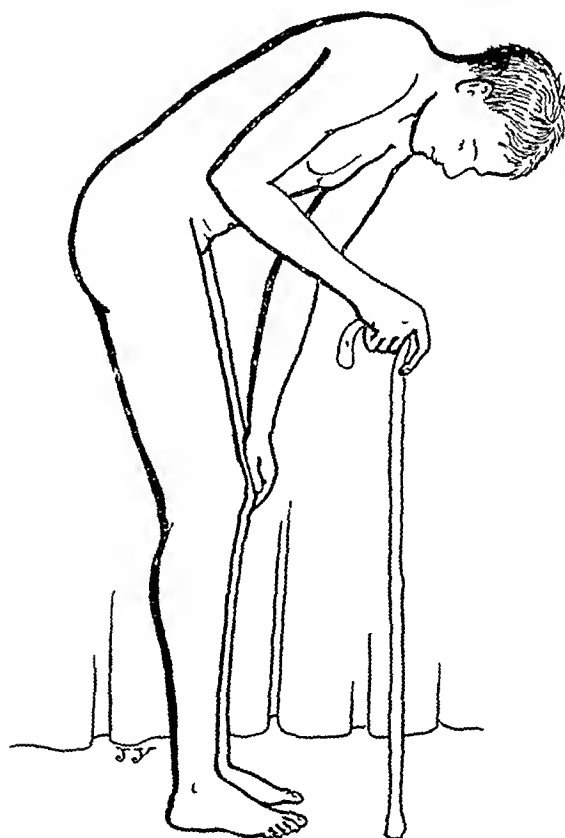


Fig 19—Same as figure 17



Fig 20—Epiphyseal coxa vara or separation of the upper femoral epiphysis which is invariably associated with adduction and external rotation deformity of the involved extremity (See figure 21)



Fig 21—Separation of the upper femoral epiphysis with adduction and external rotation attitude of the involved extremity

spines while the patient is under treatment so that the position of the pelvis may be readily recognized. It is also a fundamental principle that during the acute stage of any infection of the hip joint "the position of



Fig 22—Adduction and external rotation attitude associated with fracture of the femoral neck (See figure 23)



Fig 23—Nonunion fracture of the left femoral neck with adduction, external rotation attitude of the involved extremity

instability" (flexion, adduction, internal rotation) should be prevented and if present should be corrected to the position of stability by means of skin traction. The knee should always be supported in a position of slight flexion, since continued traction on an extremity with the knee in

complete extension is productive of hyperextension deformity of the knee or genu recurvatum

Septic arthritis of the hip joint, either primary or secondary to some remote source of infection, is in most instances associated with the position of flexion, abduction and external rotation (figs 13 and 14), although the flexion deformity may be combined with adduction and internal rotation. An attempt at traction on the involved extremity by the foot of the opposite normal extremity is frequently observed, an instinctive, unconscious effort at traction for the purpose of relieving

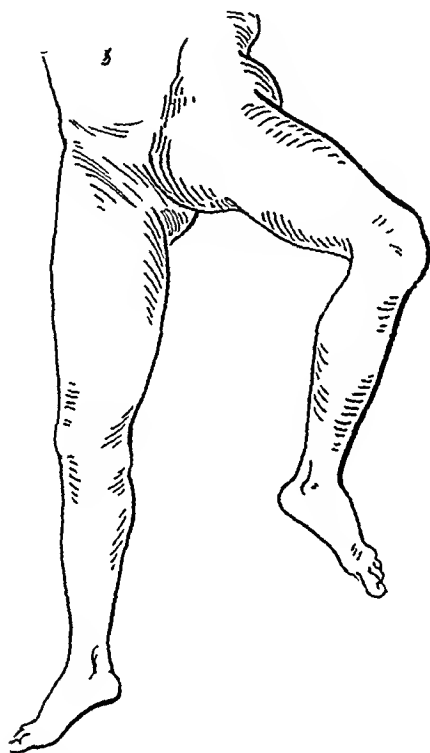


Fig 24—Flexion, abduction and external rotation attitude associated with traumatic anterior dislocation of the hip

muscle spasm and pain. Subsequent involvement of the normal hip joint in this group of cases is common, and late in the disease a bilateral infection of the hip joint is observed with the primarily involved hip in the position of stability and the hip joint of the opposite extremity, which was utilized for instinctive traction, in the position of instability. In this group with bilateral involvement of the hip joint the primarily affected hip never goes out of place, since the position is one of stability, but the hip joint of the opposite side which was placed in "the position of instability" during an effort at instinctive traction is frequently dislocated. The instinctive effort at traction by the normal extremity may also be observed during the acute stage of tuberculosis of the hip joint.

when the involved extremity is held in flexion, abduction and external rotation

Still's disease or chronic deforming polyarticular arthritis of childhood presents a constant malposition of the lower extremities. The



Fig. 25—Traumatic anterior dislocation of the hip with flexion abduction and external rotation attitude of the involved extremity

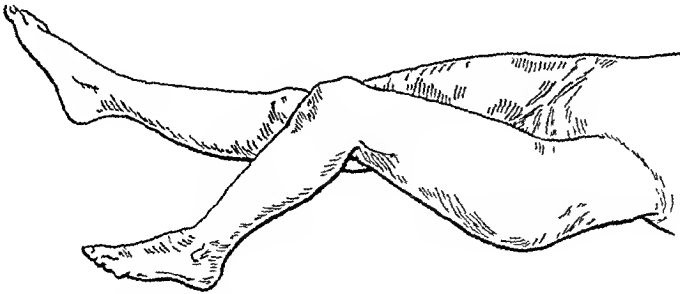


Fig. 26—Flexion, adduction and internal rotation attitude associated with traumatic posterior dislocation of the hip

hips are flexed, adducted and internally rotated. Flexion is the most prominent deformity, but adduction and internal rotation are often combined and frequently more marked in one extremity, placing it in the position of instability" which may result in spontaneous dislocation

(figs 15 and 16) Flexion and subluxation deformities of the knees and equinus deformities of the feet are also commonly associated

The attitude of an advanced case of spondylitis deformans of the rhizomelic type is also typical The dorsal and lumbar spine may be ankylosed in complete extension or greatly curved in the form of an arc When the cervical spine is ankylosed, the head may be either flexed on the trunk or in complete extension The hip joints ankylose in flexion, often associated with varying degrees of adduction The bent ankylosed position in rhizomelic spondylitis is characteristic (figs 17, 18 and 19)



Fig 27—Traumatic posterior dislocation of the hip with flexion adduction and internal rotation attitude of the involved extremity

Epiphyseal coxa vara, or separation of the upper femoral epiphysis, which invariably has its onset of symptoms during the age period of adolescence, presents a typical attitude (figs 20 and 21) The involved extremity is adducted and externally rotated Flexion deformity of the involved hip is not constant which is in contrast to the condition found in infections of the hip joint in which varying degrees of flexion are practically always found Separation of the upper femoral epiphysis is a hazard of adolescent life while fracture of the neck of the femur is a hazard of late adult life and the attitude of the involved extremity in each condition is very similar In old persons with fracture of the

femoral neck, the attitude is typical (figs 22 and 23) The extremity is adducted and externally rotated The external rotation is often marked, and when the extremity is passively rotated inward and then released it immediately returns to the former position

Traumatic dislocation of the hip joint is either anterior or posterior and each type is associated with a typical attitude Anterior dislocation is characterized by the position of abduction and external rotation with the knee flexed (figs 24 and 25) When the femoral head lies in the

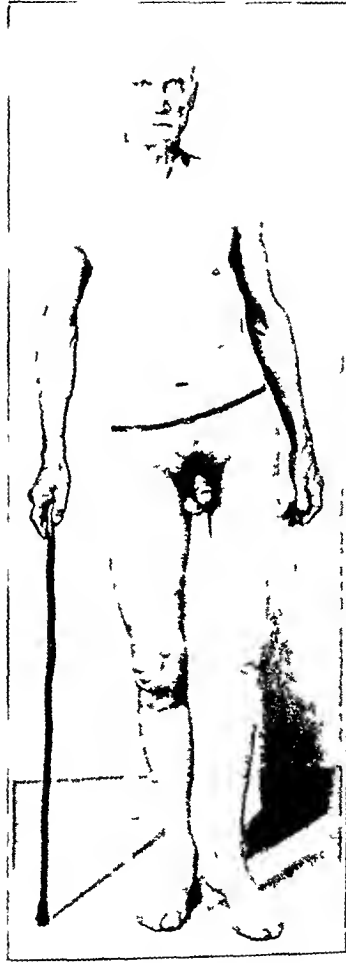


Fig 28—Flexion, adduction and external rotation associated with malum coxae senilis of the left hip

obturator foramen, the external rotation is less marked while abduction is increased If the femoral head occupies the pubic position, the external rotation is more marked and abduction is decreased There is also associated with it a mild flexion deformity Posterior dislocation presents an attitude of flexion, adduction and internal rotation (figs 26 and 27) The heel of the dislocated extremity often rests on the dorsum of the opposite foot The attitude is less pronounced when the dislocation is

of the low type with the femoral head in the region of the greater sciatic notch

Malum coxae senilis or hypertrophic arthritis of the hip joint, which appears at or after middle adult life, is characterized by the attitude of flexion, adduction and external rotation (figs 28 and 29). Flexion and adduction are the most marked features of the attitude. There is occasionally a definite history of injury preceding the onset. The history of injury during old age and the foregoing attitude may suggest fracture of the neck of the femur, but complete examination will establish the diagnosis of osteo-arthritis of the hip joint.

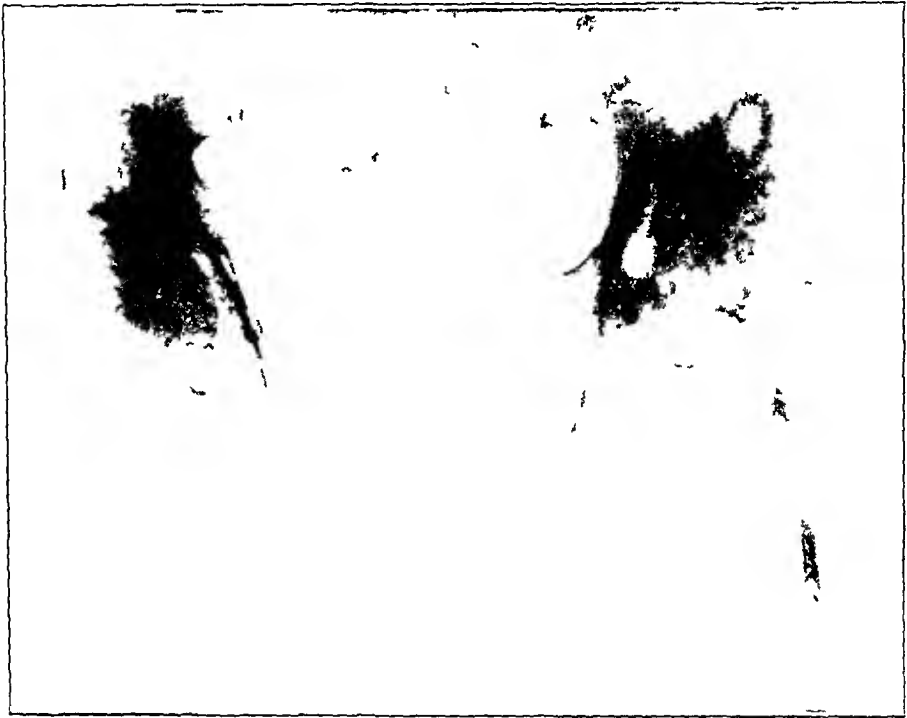


Fig. 29—Malum coxae senilis of the left hip with flexion, adduction and external rotation attitude of the involved extremity. Note the loss of joint space, sclerosis and areas of cystic degeneration of the femoral head and acetabulum.

SUMMARY

1. The attitudes of the following lesions about the hip are discussed: namely, infantile scurvy, rickets and syphilitic epiphysitis associated with pseudoparalyses; tuberculosis of the hip; spontaneous or pathologic dislocation of the hip; septic arthritis of the hip; chronic deforming arthritides—Still's disease and spondylitis rhizomelica; epiphysal coxa vara or separation of the upper femoral epiphysis; traumatic dislocations of the hip; malum coxae senilis or hypertrophic arthritis of the hip; and fracture of the neck of the femur.

2 Certain lesions about the hip joint present fairly constant attitudes of the lower extremities and have definite relations to age periods

3 There are a number of factors that determine the attitude of the lower extremities, the factors that determine the malposition in an individual case cannot always be satisfactorily explained

4 A correct interpretation of the attitude of the lower extremities cannot be made unless the pelvis is placed in the normal anatomic position with reference to the transverse and horizontal planes, and the lumbar spine is flat

5 The "frog" attitude in a child should lead the physician to suspect one of the pseudoparalyses associated with rickets, scurvy or syphilitic epiphysitis

6 "The position of instability" of the hip joint (flexion, adduction, internal rotation) is productive of spontaneous dislocation and should be considered a dangerous attitude

7 Epiphyseal coxa vara is a hazard of adolescent life, and fracture of the neck of the femur is a hazard of old age. The attitude of the involved extremity in each condition is similar, i. e., adduction and external rotation

8 Infection of the hip joint presents a constant malposition of flexion combined with either abduction and external rotation or adduction and internal rotation

SPONDYLITIS DEFORMANS

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One of the greatest advances in orthopedic surgery is the development and application of preventive measures in the control of deformities, particularly those of the spine. Because of familiarity with the progress and end-results of certain diseases, it is possible to institute treatment to forestall severe deformities and their inevitable accompanying functional derangement. One is no longer content to watch a case of structural scoliosis, for instance, treated by antiquated therapy, progress to a degree of deformity which is both grotesque and disabling. By a well planned spinal fusion, the mild and moderate grades of scolioses may be prevented from becoming worse, thus assuring the patient an acceptable appearance and physical fitness. Similarly, the progressive deformity of spondylitis deformans may be checked if the disease is recognized in its incipency and the proper course of treatment immediately instituted. The purpose of this communication is to call attention to the clinical aspects and to the most effective form of treatment in cases with increasing deformity.

Spondylitis deformans is a progressive disease of the spine characterized by gradually increasing flexion of the trunk and ankylosis of the vertebrae. The disease may come on insidiously, but it usually begins suddenly with pain and stiffness of the back, resembling an attack of so-called lumbago. The pain may be limited to one part of the spine, or may be general throughout the back. It may radiate to the head, chest, abdomen or to the extremities. At first the symptoms appear at intervals of varying duration, with intermissions, during which the patient is free from discomfort and stands and walks erect. Injury or illness may aggravate the symptoms. If the patient is examined during the first year or two after the onset, it will be found that he stands and walks with his head bent forward. The back is symmetrical but flat. There is a loss of the normal lumbar hollow, and the spinal motions are moderately or markedly limited. If asked to straighten up, the patient sways his trunk backward until his eyes look forward. The surgeon can, however, readily detect that in this act there is only slight motion in the spine itself, the trunk being hyperextended on the hips. There is

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moderate spasm of the trunk muscles, but no tenderness of the vertebrae. When the trunk is bent forcibly in any direction, there is considerable pain. This is, I believe, a significant observation, indicating inflammatory irritation of, or in the vicinity of, the vertebrae. An x-ray film of the spine may be entirely negative or may show marginal lipping or osteophytes. This may not excite special interest, unless one suspects the true nature of the lesion and anticipates that continued growth of the bony spurs will cause fusion of the vertebrae. Because of the slow progress of the disease and the frequent remissions and periods of well being, the attention of both the patient and his physician does not become focused on the spine until there is a definite resistant deformity. When the orthopedic surgeon is consulted, several years have usually elapsed since the onset of the symptoms, there are well marked clinical evidences



Fig 1—A patient with an advanced degree of spondylitis deformans. The trunk is fixed in flexion. The chest is flat and the abdomen prominent. There is marked increase in the dorsal backward curve. The head is held forward. The patient cannot look up except by bending the trunk backward on the hips. Note the crease across the abdomen indicating flexion of the trunk.

of grave disturbance of the function of the spine, and the x-ray films reveal the beginning of ankylosis of the vertebrae.

At a later stage there is increasing deformity with stiffness of the back and weakness of the back and legs. The trunk appears bent on itself (fig 1). There is a forward thrust of the head, so that the eyes are continuously directed downward. There is a marked increase in the backward curve of the dorsal area and flattening of the lumbar spine. The lower part of the chest is depressed. The lower part of the abdomen bulges and there is a deep crease across the upper part of the abdomen indicative of fixed flexion of the spine. The fixed flexion deformity becomes especially noticeable when the patient lies on his back. When the lumbar area is flat on the table, the head is from 4 to 8 inches (10.16 to 20.32 cm) away from the table. The gait is

awkward because of the rigidity of the spine during every motion of the body. Ultimately the spine becomes completely ankylosed, so that the patient has what is called a "poker back." He is usually able to move his head backward and forward a little because the occipito-atloid

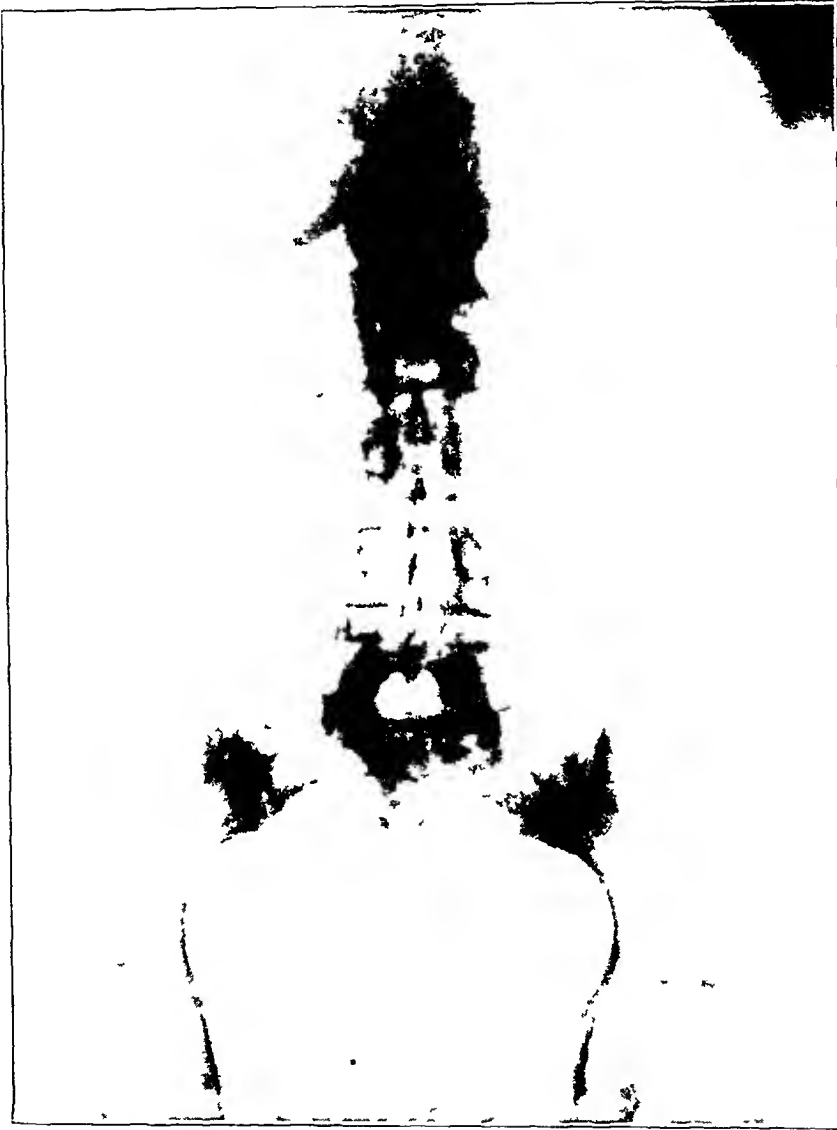


Fig 2—Anteroposterior view of the lumbar spine in a case of advanced spondylitis deformans showing complete bony ankylosis of the spine by bilateral intervertebral bridges of bone

joints are rarely involved, but he cannot move his head sideways, nor bend his spine forward, laterally or in a rotary direction. The ribs may become fixed through ankylosis of the costovertebral joints, so that breathing is entirely abdominal. The general health of the patient is very poor, and he suffers much from headache and neurasthenia. The

backache disappears when the vertebral ankylosis is complete, but the pain in the limbs may continue indefinitely because of the pressure of the newly formed bone on the nerves at their exit from the intervertebral foramina

Spondylitis deformans may occur in one of three forms (1) as an independent disease (most frequent type), (2) as part of a general polyarthritis and (3) in association with involvement of the hips or shoulders. It occurs much more frequently in males than in females, and usually between the ages of 20 and 40. Its causes are numerous, and many of them are not thoroughly understood. In general, three etiologic types may be distinguished: (1) that which is part of a general metabolic disturbance, (2) the traumatic variety and (3) the infectious group. In the latter type are such well known causes as typhoid and gonorrhea.

The chief pathologic change is a chronic progressive ossifying periostitis of the spine which leads to ankylosis of the vertebrae and the costovertebral joints. This process may affect a limited area, but it usually involves the entire spine, and is apparently the same irrespective of the particular etiologic factor. The new bone in the advanced stage of this disease, according to Jones and Lovett, appears in the x-ray picture like callus that has been melted and allowed to run down the front and sides of the vertebral column (fig. 2).

TREATMENT

The treatment is general and local. The general treatment is directed toward removing or remedying whatever etiologic factor or focus of infection is discovered, toward improving the health of the patient and toward relieving him of pain. So far as focal infection is concerned it has been my experience that one can rarely discover a source of infection that may with certainty be considered the real cause of the spinal disease. Furthermore, removal of infectious foci, such as diseased tonsils or teeth, does not usually have a beneficial effect on the vertebral lesion. This fact was emphasized in a recent article on spondylitis deformans by Dr. Nachlas¹ of Baltimore. In the foregoing thought, I do not mean to convey the impression that spondylitis deformans is not dependent on some infectious process. But, thus far, I have been unable, except in a few cases in which the disease was evidently of typhoid or gonorrheal origin, to identify definitely the causative factor.

The local treatment is directed to the back and has practically no relation to the cause of the disease. The local treatment of spondylitis

¹ Nachlas, William. Focal Infection in Spondylitis Deformans, *Arch Surg* 20: 159 (Jan.) 1930.

deformans is concerned first, with the correction of the deformity, secondly, the mobilization of the spine whenever possible, and thirdly, the relief of backache. When the condition of the patient has progressed to the stage of complete bony ankylosis of the vertebrae, the deformity and disability are permanent and irremediable. However, during the earlier stages, and for a long time before the ankylosis is complete and absolute, there is ample opportunity to apply treatment effectively. Though the patient may present what appears to be clinically complete rigidity and fixation of the entire spine, if the x-ray picture shows no bony ankylosis or complete fusion of only some of the vertebrae or partial fusion of several small spinal segments, I am encouraged to apply treatment in the hope of arresting the process and, more particularly, of correcting the existing deformity. It is this phase of spondylitis

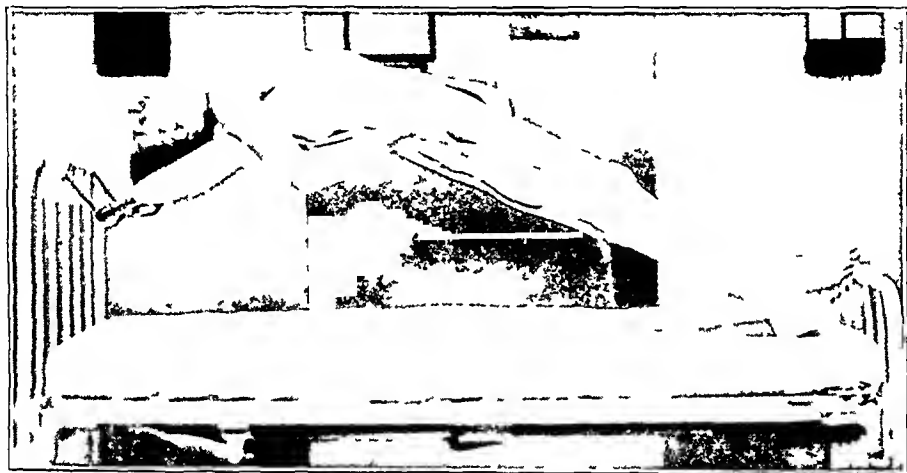


Fig 3—Patient with spondylitis deformans resting on a convex frame. This attitude of hyperextension is attained only after several weeks of treatment on a frame which at first is flat and later is gradually made convex.

deformans that has interested me especially, and I shall discuss at length the local treatment which has proved of great value.

The essential element in the treatment is continuous rest in the supine position, first on a straight frame and later on a convex frame (fig 3). In this attitude the muscles relax, the discomfort disappears, and the spine gradually adapts itself to the curve of the frame. The treatment is slow and prolonged. Both patient and surgeon must be prepared to spend from two to six months in attaining their object. The treatment can best be carried out in a hospital equipped with a brace shop for the manufacture of the frame and for the frequent changes in its angulations. The treatment is most conveniently carried out in an orthopedic institution, where everybody concerned is accustomed to chronic cases and the care of this type of patient, who needs much patient nursing,

The frame is rectangular, made of gas pipe and covered with tightly stretched canvas. It is the ordinary convex frame used for scoliosis, round shoulders and Pott's disease, except that it is several inches wider than the distance between the patient's shoulders, so that his arms may rest comfortably on the canvas. Twenty inches (50.8 cm) is an average width. The length of the frame is sufficient to allow it to extend about 4 inches (10 cm) above the patient's head and at least as much below his feet. The frame may rest on the mattress or be suspended from the head and foot pieces of the bed.

Usually the patient cannot be placed on the frame immediately, because the spine is so stiff that it cannot adapt itself to the position of extension. Consequently, he is first placed in bed and urged to stay on his back as nearly continuously as possible. Several times a day he turns on one or the other side for relief from the supine position. After a few days he is placed on a frame that has a gentle curve of approximately 5 degrees. Several days later the curve of the frame is increased by 5 or 10 degrees, and every four or five days thereafter the angle of the frame is slightly increased. The change in the curve of the frame depends on the tolerance of the patient and his ability to arch his back in conformity to the convexity of the frame. In the average case, one can expect to increase the angle of the frame to 45 degrees in about four to six weeks. There are at present two frames that are particularly useful in gradually hyperextending the spine. One is that devised and described by Dr. M. H. Herzmark.² His frame is adjustable as to length and width and has a joint on each side. The frame is adjusted so that the joint is opposite that part of the back where one hopes to get the greatest convexity. The curve of the frame is controlled by a turn-buckle connected by long levers to the ends of the frame. This frame is especially useful for cases of spondylitis deformans, as at first it may be made concave forward and thus make a comfortable bed for the patient with a flexed spine. Then without removing the patient, the curve of the frame may be changed slowly and as gradually as may be necessary, so that the concavity is ultimately converted into a convexity. A convexity of nearly 60 degrees may be obtained on the Herzmark frame. The other is the frame devised by Dr. Charles Rogers of Boston. It is a very ingenious apparatus. By an arrangement similar to an automobile jack, the convexity of the frame can be gradually increased without removing the patient.

During the period of active treatment on the frame, the back receives baking and massage. The patient is also encouraged to exercise his limbs and his back. Several times a day he changes to the supine position.

² Herzmark, Maurice H. An Adjustable Convex Frame, *J. Bone & Joint Surg.* 11: 794 (Oct.) 1929.

tion, places his hands behind his back and forcibly arches his back until he can look up at the ceiling. It is surprising how much the patient can accomplish by persistent effort. The extension and ultimate hyperextension of the spine can be materially increased by judicious daily passive movement or stretching of the spine. This procedure should not be left to a masseur, who in his desire to bring improvement may use too much force and set up a painful irritation of the spine which will retard the improvement. The surgeon in charge should stretch the patient's back. He knows what he seeks to obtain by treatment, he has studied and understands the patient, and is in a position to appreciate best the degree of force and the duration of the treatment that may be safely employed to effect a correction of the deformity. When the spine can be arched backward voluntarily to a normal or nearly normal angle, one begins to move the spine laterally and in a rotatory direction.

One aims for a complete correction of the deformity. Sometimes, however, because of the severity of the disease process, a cure is impossible, and one must be content with only an improvement. The corrective measures are continued until there is no further change despite the use of strenuous force.

When a cure or the maximum improvement has been obtained, the patient is left on the frame several weeks longer to assure the permanency of the result. In the meantime, he is measured for a Taylor spinal brace. This is preferred to other spinal supports, because it fixes the shoulder and pelvic girdles while exerting corrective pressure on the dorsal area. When the brace has been applied, the patient is allowed to sit up or stand for brief periods. Gradually the period out of bed is extended until the patient is able to be about for several hours a day. He can then be discharged from the hospital and the treatment completed at the patient's home, in the physician's office or, in the case of a service patient, in the dispensary. The local treatment to the back should be kept up for many months.

During the greater part of the day the patient lies on the convex frame. When out of bed, he wears the spinal brace. He must continue with massage, stretching of the back and corrective exercises. The surgeon cannot relax his efforts until there is definite evidence over a period of many months that there is no tendency to relapse of the deformity.

REPORT CASES

CASE 1—W. L., aged 21, was admitted to the hospital on Dec. 22, 1927. His chief complaint was of pain and stiffness of the back, pain in the shoulders and weakness of the lower limbs. About two years previously he fell a distance of 15 feet, striking the ground in the sitting position. One month later he began to have pain in his back and right hip. The stiffness of his back began one year before admission to the hospital and gradually increased, so that at the end of

six months he was unable to bend sideways, forward or backward. During the last few months he tired easily and was unable to lift objects from the floor. Later he had pain in both shoulders. His past history was unimportant, except that he had had the ordinary diseases of childhood and at the age of 8, typhoid fever.

On admission to the hospital, he presented every evidence of spondylitis deformans. He was in poor general condition. He stood and walked with his body inclined forward (fig 4). His gait was awkward. There was stiffness and loss of mobility in the dorsal and lumbar areas, with a marked increase in the dorsal curve and flatness in the lumbar region. The cervical spine was

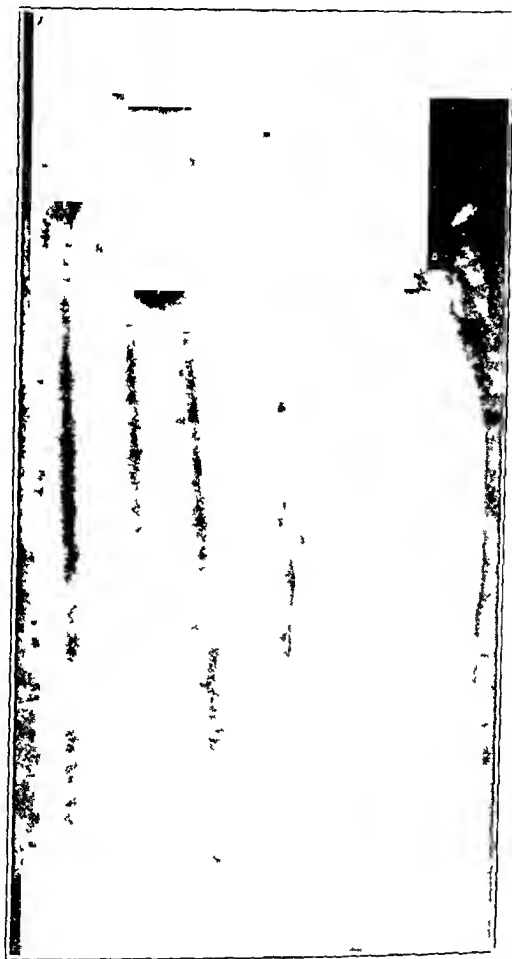


Fig 4 (case 1)—W L, on admission, showing the typical attitude of a person with moderate grade of spondylitis deformans. The head is thrust forward. There is an increase in the posterior curve of the dorsal area. The lumbar region is flat.

freely movable, and neither the shoulders, hips, nor any of the other joints were involved. The x-ray pictures of the spine showed little positive change in the vertebrae. The Wassermann and gonococcus fixation tests were negative.

This patient evidently had a spondylitis deformans in which only the spinal joints were involved. The disease probably resulted from the injury sustained two years previously. There was no evidence of any infectious bacterial agent. The attack of typhoid fever, noted in the history, occurred so long ago that it probably had no relation to the spinal lesion. Although the x-ray pictures showed

no ankylosis the spine was rigid, and the patient had a well marked flexion deformity of the trunk. This patient was at a stage in his disease when treatment could not only correct the existing deformity, but prevent future distortion of the spine. Accordingly, he was given the treatment outlined. He was kept on a convex frame for several months. The backache and the pains in the limbs disappeared, and the deformity was corrected. He was discharged wearing a Taylor spinal brace (fig 5), with the trunk restored to the normal attitude.

CASE 2—Max B, aged 35, was seen in February, 1928. His chief complaint was of stiffness of the back and curvature of the spine. The known duration was



Fig 5 (case 1)—W L, at the end of the hospital treatment, showing correction of the deformity. He is wearing the Taylor spinal brace, which maintains the attitude of extension of the spine obtained by treatment on a convex frame.

three years. He was a tailor and had always sat with his body bent forward. His symptoms were initiated by pain across the lower part of the back. Gradually, his back became stiff.

This patient was underweight and in poor general condition. His spine was curved backward markedly in the dorsal region and was flat in the lumbar area. His trunk was fixed in flexion. There was complete immobility of the dorsal and lumbar vertebrae. In the cervical segment of the spine there was slight motion which was very painful. No other joints were affected. The x-ray pictures of the spine showed an increase in the dorsal curve and an obliteration of the lumbar lordosis. There were no osteophytes or bony bridges between any of the vertebrae.

This was a case of extreme spondylitis deformans due, probably, to many years of faulty posture. All of the vertebrae, including those in the cervical area, were affected. Since there was no bony ankylosis, as evidenced by negative x-ray pictures, the prognosis was favorable and one might expect to correct the deformity completely by the postural treatment outlined.

CASE 3—Mrs. K. was seen by me in January, 1929. She complained of deformity of the back, pain in the right thigh and a limp on the right side. Four years previously, following the birth of her second child, she began to have backache. This gradually increased, and her back became increasingly deformed. Examination showed that she had a marked degree of spondylitis deformans. Her spine was bowed backward, her head was held forward. There was complete rigidity of the spine and loss of mobility in all of the intervertebral joints, except that between the occiput and the atlas. There was enough motion in the occipito-atloid joint to permit flexion and rotation of the head. In addition, she had marked involvement of the right hip joint. The limb was flexed to an angle of 150 degrees. There was about 40 degrees of flexion, practically no abduction, and only a few degrees of rotation. The x-ray pictures showed a very advanced osteo-arthritis of the right hip and of all of the vertebral joints. In this case the arthritic process in the spine was associated with an arthritis in the right hip.

CASE 4—A. Y., aged 65, had pains in all of her joints for fifteen years. During the last five years she has suffered more particularly from pain in her back and in her knees. Examination showed that she had complete immobility of the dorsal and lumbar vertebrae, marked backward bowing in the dorsal area and flatness in the lumbar region. The motions in her cervical spine were limited to about half of the normal. She had a very marked degree of arthritis in both sacro-iliac joints, in both shoulders, in the fingers, in both hips and in both knees. In this case the spondylitis was part of a generalized arthritis.

The foregoing four cases were chosen as representative of the different types of spondylitis which one encounters. They have also been cited in the order of frequency with which one sees the different lesions associated with spondylitis deformans.

SUMMARY

To review briefly the preceding considerations. Spondylitis deformans is a chronic disease of the back characterized by increasing stiffness and deformity of the spine, backache, pains in the head, chest or extremities, headache and impairment of health. Although there are numerous causes of this disease, the final pathologic change is the same in all varieties. The most disabling feature of this disease is the flexion deformity of the spine. Treatment to be effective must be instituted before there is complete bony ankylosis of the spine. The deformity can be corrected, or at least reduced, by continuous treatment on a convex frame, supplemented by physiotherapy, stretching of the back and voluntary corrective exercises. Following the correction of the deformity a favorable result can be assured only by a long period of support of the back in a spinal brace.

THE EFFECT OF ATELECTASIS ON THE PULMONARY BLOOD VOLUME *

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AND
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Heretofore, the methods used for measuring the effect of various types of atelectasis on the pulmonary circulation have been too indirect to justify positive assurance as to the actual quantitative variations in blood volume that occur in a lung as a result of pneumothorax or bronchial obstruction. The evidence available is adequately reviewed in the recent exhaustive article by Coryllos and Birnbaum.¹ In support of the ischemic effect of obstruction atelectasis, these authors offer further evidence by perfusion experiments of the lungs with india ink. Microscopic examination of the atelectatic lung, with the interalveolar capillaries rendered visible by this method, shows by comparison with the normal lung a marked decrease in the number of capillaries per unit of parenchyma. From this they conclude that the blood content per alveolar sac and, therefore, for the whole lung is less than for a normal lung. With Bruns,² who used a colorimetric method of measuring the relative amount of blood in the sound and in the collapsed lung, they agree that the decrease in blood capacity is proportionate to and "regulated by" the degree of collapse.

Since the physiologic mechanism underlying the success of modern collapse therapy is not yet clearly understood, it seems that a direct quantitative determination of the total blood and lymph flow in a collapsed lung would lead to an elucidation of the factors involved in the obviously effective measures now in use.

This report deals with a method, adapted from one published in 1923 by Drinker, Shaw and Drinker,³ of obtaining such quantitative data as

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^ From the Department of Physiology, Harvard School of Public Health, and the Beth Israel Hospital.

1 Coryllos, P. N., and Birnbaum, G. L. Circulation in Compressed Atelectatic and Pneumonic Lung. *Arch. Surg.* **19**: 1346 (Dec.) 1929.

2 Bruns, O. *Arch. f. klin. Med.* **108**: 469, 1912. *Beitr. z. Klin. d. Tuberk.* **12**: 1, 1909.

3 Drinker, C. K., Shaw, L. A., and Drinker, K. R. *J. Exper. Med.* **37**: 829, 1913.

fa1 as the blood flow is concerned. They were able to quantitate accurately the amount of manganese deposited in various organs of the cat following intravenous injection of a suspension of manganese dioxide or manganese silicate particles. But it was felt that for the purposes of this study a colloidal solution of a nontoxic, insoluble, non-diffusible substance, which could be used as a perfusate and accurately quantitated, would be preferable. Colloidal nickel sulphide (solubility 0.003 mg per liter 20 C) was employed because Fairhall,⁴ in 1926, published a reliable method for the quantitative estimation of nickel in biologic material.

The following experiments give as direct evidence as it seems possible to obtain that atelectasis, whether induced by pneumothorax or bronchial obstruction, definitely and markedly decreases the total blood volume of the affected lung.

Three series of experiments were carried out: the first, to determine the normal ratio of total blood volume of the two lungs, the second, to observe the effect of a partial or complete compression atelectasis (pneumothorax) on this ratio, and the third, to observe the effect of a total obstruction atelectasis (bronchial ligation) on this ratio. The rabbit was used for all the experiments, chiefly because of its relatively rigid and imperforate mediastinum as compared with other laboratory animals.

METHOD

All experiments were carried out under intraperitoneal barbital anesthesia.

The nickel sulphide perfusate was prepared as follows. "Nickel sulphide, C. P." (Eimer and Amend) was repeatedly washed with distilled water until all of the soluble nickel salts present were removed. An excess of this was shaken up with a liter of 5 per cent solution of purified acacia brought to a pH of 7.4 and allowed to stand. The supernatant colloidal solution of nickel sulphide was siphoned off and used for intravenous injection. This solution is stable and runs from a buret without leaving the slightest trace of precipitate on the sides of the tube.

The first series of six rabbits were treated as follows. A cannula was inserted in the left carotid artery, and another, connected to a buret containing the perfusate, was inserted into the right jugular vein. The animal was bled, and, when about half exsanguinated, the perfusate (from 50 to 100 cc) was slowly run into the vein until the blood from the carotid artery was practically black, soon after which the animal died. The trachea was then clamped, the chest opened, both lungs ligated in situ at the hilus, and then removed, no fluid escaping from any part of the vascular system until the lungs were cut away proximal to the site of the ligature. The entire vascular system in these rabbits seemed to contain the perfusate mixed with a small proportion of blood. There was no evidence in the lungs or other tissues that any of the nickel sulphide had entered the tissue spaces by penetrating the capillary walls. All six animals showed an even diffu-

4 Fairhall, L. T. J. Indust. Hyg. 8: 528, 1926.

sion of the nickel sulphite throughout their lung surfaces. An uneven diffusion occurred in a number of animals not included in this series, probably because of insufficient bleeding. These were discarded as unsatisfactory and were not analyzed.

Each lung was quantitatively analyzed for metallic nickel, which was taken as a measure of the total blood volume of the lung. The results showing the normal ratio of total blood volume of right and left lungs are given in table 1.

The second series of animals were treated in the same way, but were previously subjected to pneumothorax. This was accomplished by injection of air, in amounts varying from 30 to 50 cc, into the pleural space, a water manometer being used as a guide, so that in all but two or three cases no positive intrapleural tension was present when the pneumothorax was completed. The degree of collapse resulting was not proportionate to the amount of air introduced. The reason for this is not clear, but those cases in which the air was slowly injected were usually more completely collapsed. In several animals not listed in the tables, the lung was reduced in size to far below that seen in full expiration without showing the liver-like consistency of atelectasis.

TABLE 1—*Ratio of Total Blood Volume of Right and Left Lungs in Terms of Milligrams of Metallic Nickel*

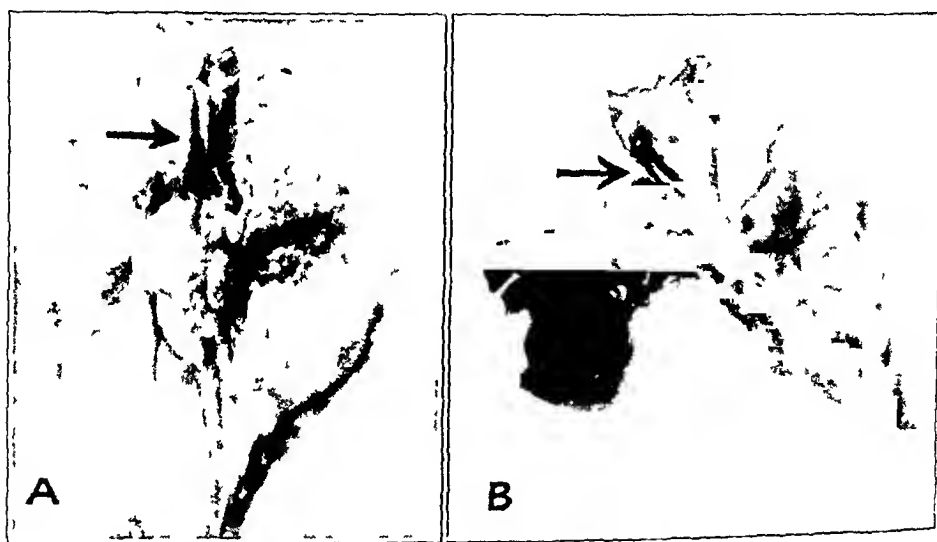
Experiment	Ratio, Mg		Ratio Per Cent	
	Right Lung	Left Lung	Right to Left	Left to Right
1	0.717	0.400	179.2	55.7
2	0.750	0.475	157.8	63.3
3	0.715	0.500	143.0	69.9
4	0.450	0.250	180.0	55.5
5	0.170	0.250	188.8	53.2
6	1.500	1.065	140.8	61.1
			Average 164.9	59.7

The perfusion in these animals was carried out within from ten minutes to half an hour following the induction of the pneumothorax. Following the induction, some of the animals were slightly cyanotic, some showed hyperpnea or tachypnea and others seemed to be apparently unaffected.

The third series was carried out in order to compare the effect of compression atelectasis with obstruction atelectasis. For this purpose preliminary ligation of a primary bronchus was done by way of the superior mediastinum. A tracheal cannula was connected to an artificial respiration apparatus, and the mediastinum exposed by splitting the sternum in its upper two-thirds. The thymus was lifted up from the pericardium, the aorta retracted to the left and the superior vena cava to the right, and a ligature was applied to the right primary bronchus after it was carefully isolated from all other structures. In certain cases the mediastinal pleura was not opened, but as a rule the right mediastinal pleura was unavoidably torn in lifting the thymus up and out of the way. Before the ligature was tightened, the lung was distended just enough to fill its entire pleural space so as to avoid any compression atelectasis. In order to save the time necessary for absorption of intra-alveolar nitrogen, pure oxygen was fed into the lungs for some minutes before the ligature was applied. As soon as the ligature was applied the chest was closed the last ligature being tied at the height of an inspiratory stroke of the artificial respiration machine. The animal was then allowed to breathe air spontaneously, but in a few cases it was necessary to con-

tinue artificial respiration until the experiment was completed. The perfusion was carried out without much waiting, because it was noted in several preliminary experiments that not more than a few minutes were necessary to produce a total atelectasis when the lung contained pure oxygen before application of the ligature. This was not the case when air was breathed before bronchial ligation (see illustration).

Van Allen and Adams⁵ have recently reported their inability to produce atelectasis in a normally breathing animal subjected to total bronchial obstruction. They consider that straining respiration is essential. The time necessary to absorb the incarcerated nitrogen seems to be the important factor. Andrus⁶ obtained total atelectasis in three days, and Coryllos and Birnbaum¹ secured the same result in twenty-four hours.



Lungs removed one-half hour after ligating the right primary bronchus in the rabbit. In *A*, the animal was breathing air before ligation, result, no atelectasis, in *B*, it was breathing oxygen before ligation, result, total atelectasis. The arrows point to the ligature on the right primary bronchus.

In both the second and the third series, as in the first, no animal was used for analysis that failed to show an even diffusion of nickel sulphide throughout the lungs.

COMMENT

From table 1, it is evident that the rabbit's right lung has an average of 164.9 per cent total blood volume as compared to the left lung. The variations from this mean do not appear too excessive to make the average result far from the truth.

⁵ Van Allen, C. M., and Adams, W. E. *Surg. Gynec. Obst.* **1**: 385, 1930.

⁶ Andrus, W. de W. *Cardiorespiratory Physiology Following Collapse of One Lung by Bronchial Ligation*, *Arch. Surg.* **10**: 506 (Jan.) 1925.

From the upper half of table 2, it appears that a partial atelectasis of varying degree, roughly estimated by surface inspection, in the right lung reduces the normal ratio of blood volume of the right lung as compared with the left from an average of 164.9 per cent to one of 122.3 per cent—a reduction in total blood volume in the right lung of 25.9 per cent.

It is obvious that the actual amount of nickel present in the different animals varies considerably. This is due to the varying concentration of the nickel sulphide particles in the different samples of perfusate made up for injection and to the varying degrees of exsanguination in

TABLE 2—*Effect of Partial to Complete Compression Atelectasis of the Lung on Its Total Blood Volume Measured in Terms of Milligrams of Metallic Nickel*

Lung Com-pressed	Experiment	Air Used for Pneumothorax, Cc	Extent of Atelectasis Obtained	Amount of Metallic Nickel, Mg		Ratio, Per Cent	
				In Right Lung	In Left Lung	Right to Left	Left to Right
Right	1	50	Partial (about $\frac{1}{3}$ complete)	0.163	0.113	144.4	69.2
	2	40	Partial (about $\frac{1}{2}$ to $\frac{2}{3}$ complete)	1.250	1.000	125.0	80.0
	3	35	Partial (about $\frac{2}{3}$ complete)	0.625	0.563	111.1	90.0
	4	35	Partial (about $\frac{3}{4}$ complete)	0.625	0.500	125.0	80.0
	5	40	Partial (about $\frac{1}{2}$ to $\frac{1}{2}$ complete)	0.900	0.700	128.5	77.7
	6	40	Partial (degree not noted)	0.750	0.750	100.0	100.0
Average						122.3	82.8
Left	7	45	Partial (about $\frac{1}{3}$ complete)	0.750	0.400	187.5	53.3
	8	35	Complete	0.750	0.563	133.2	75.0
	9	Undetermined *	Complete	9.750	5.000	195.0	51.2
	10	Undetermined *	Partial (about $\frac{2}{3}$ complete)	11.880	5.020	236.6	42.2
	11	30	Complete	9.750	1.450	672.4	14.6
	12	30	Complete	7.500	0.813	923.0	10.8
Average						591.3	41.2

* Pneumothorax induced by small opening in pleura and closed after several inspirations.

the different animals. Except for experiment 1, table 2, in which the small amounts of nickel present may, because of the greater chance of error in quantitative analysis, account for the rather wide variation from the average ratio, the results show a fairly satisfactory approximation to the average.

It is also evident that the amount of reduction in blood volume of the compressed lung bears no close relation to the extent of the atelectasis obtained. This may be due to an uneven distribution of the air in the pleural space, producing a widely distributed compression effect on the capillaries without evenly collapsing the alveoli in all directions.

In the lower half of table 2, except for experiments 7 and 8, the left lung totally atelectatic in most cases, shows a very considerable

but greatly varying, reduction in blood volume as compared with the right lung, as is evident from the change in the relative blood volumes of the two lungs in favor of the right lung. In experiments 7 and 8, this change has not occurred. It should be stated that in both of these animals the right lung on removal was very emphysematous, which was not the case in any of the other animals in all of the series. That this interfered with the transference of the excluded blood from the left lung into the capillaries of the right lung is possible. At least, so far as experiment 8 is concerned, in which the result is altogether at variance with the rest of the series, it should be added that the heart failed during the middle of the perfusion and may have thus interfered with the transference of the blood excluded from the left lung into the right. For it is assumed that in collapse of one lung the total pulmonary blood flow is not greatly altered unless the right ventricle fails (Dock and Harrison⁷).

Here again, as in the first six animals, the reduction in blood volume is by no means in direct proportion to the amount of atelectasis obtained, which was complete in three of the last four animals in the series. This, also, may perhaps be accounted for on the basis of varying degrees of intrapleural tension, causing different degrees of capillary compression. In one animal not included in the series, the pneumothorax compressed the left lung tightly against the spine and reduced its size to not more than one-half the volume expected in full expiration, without producing more than a few small islands of atelectasis. In spite of the absence of atelectasis, the blood content of the left lung was 0.75 mg. as compared with 3.43 mg. in the right—a decrease in the left lung of 63.4 per cent of the average normal.

The more complete atelectasis obtained in experiments 8 to 12 was probably due to the introduction of air more slowly than in experiments 1 to 6. The much greater quantities of nickel present in experiments 9 to 12, inclusive, are due to the use of a far more concentrated perfusate and possibly, to some extent, to a more complete exsanguination of the animal.

The average decrease in total blood volume of the left lung (completely atelectatic in four of six cases, experiments 7 to 12, inclusive) is 31 per cent. If, however, experiments 7 and 8 are excluded, the average decrease is 54.5 per cent. Comparison of this with a 25.9 per cent decrease in partial atelectasis of the right lung gives evidence in favor of the contention of Bruns² that the reduction in blood volume of the lung is directly dependent on the degree of atelectasis.

⁷ Dock, W. and Harrison, T. R. *Am. Rev. Tuberc.* **10**: 534, 1924-1925.

Dock and Harrison⁷ agreed with Cloetta⁸ that hyperemia is found immediately following collapse, on the basis of their observation that from 52 to 58 per cent of the total pulmonary blood volume flows through the collapsed right lung during the first few hours following induction of pneumothorax. They stated that it takes a longer time than this for the lung to become atelectatic. In our experiments, the interval between the induction of pneumothorax and the removal of the atelectatic lung after perfusion did not exceed thirty minutes and often was much less, so that their defense of Cloetta's observation cannot be sustained. The normal blood volume of the right lung in their experiments may have actually been more than from 52 to 58 per cent of the total, so that in fact these figures may represent a reduction in the blood volume of the collapsed right lung.

TABLE 3—*Effect of Absorption Atelectasis on Total Blood Volume of Affected Lung in Terms of Milligrams of Metallic Nickel*

Experiment	Primary Bronchus Ligated	Amount of Metallic Nickel Mg		Ratio Per Cent	
		In Right Lung	In Left Lung	Right to Left	Left to Right
1	Right	0.375	0.563	66.6	150.0
2	Right	0.438	0.750	58.3	172.0
3	Right	1.500	1.500	100.0	100.0
4	Right	1.375	1.750	78.5	127.2
5	Right	1.188	1.500	79.1	126.3
6	Right	1.000	1.125	80.0	112.5
7	Right	1.125	0.750	150.0	66.6
		Average		87.5	122.1

The conclusions of Corper, Simon and Rensch,⁹ to the effect that no decrease in circulation occurs shortly after collapse, are likewise not supported by the results shown in table 2.

These observations, along with the microscopic evidence offered by Coryllos and Birnbaum, agree with Gardner's¹⁰ pathologic studies on human lungs to the effect that pneumothorax produces a compression of the capillary bed.

The third series of experiments summarized in table 3, deal with absorption atelectasis. It was thought desirable to compare the effect of absorption obstruction atelectasis with compression atelectasis, in order to eliminate the factor of capillary compression by extrapulmonary pressure.

In seven experiments detailed in table 3, the totally atelectatic right lung showed a total blood volume which was only 87.5 per cent of the

⁸ Cloetta, M. Arch f exper Path u Pharmacol **66** 409, 1911.

⁹ Corper, H. J., Simon, S., and Rensch, O. B. Am Rev Tuberc **4** 592, 1920.

¹⁰ Gardner, L. U. Am Rev Tuberc **10** 510 1924-1925.

left, a reduction from the normal blood volume of 46.9 per cent. The seventh experiment in the series gives a result that is only explainable as an error, probably in the chemical analysis.

SUMMARY

It appears, therefore, that partial to complete atelectasis induced by pneumothorax at once reduces the total blood volume of the affected lung by amounts varying, on an average, between 25.9 to 54.5 per cent, and in individual cases by a considerably higher percentage. Absorption atelectasis reduces the total blood volume of the affected lung by 46.9 per cent.

In the former type of atelectasis the reduction is not dependent only on the actual amount of atelectasis obtained. An additional factor is the amount of compression induced. Thus, in no case of total absorption atelectasis was there such a large reduction as was obtained in experiments 11 and 12 (75.6 and 82 per cent, respectively), table 2, of the compression atelectasis series. Hence, the actual reduction probably depends on the variable factor of intrapleural tension in addition to the atelectasis per se. Although the extent of the atelectasis obtained is not necessarily proportional to the amount of compression, nevertheless, the reduction in blood volume is, in general, greatest when the atelectasis is complete.

Whether the reduction in blood volume in either type of collapse aside from the added effect of the extrapulmonary compression of the capillaries in the pneumothorax type, is due to the shrinkage of the capillaries purely because of alveolar collapse or to some other factor will be the subject of the next report. In the experiments made to ascertain this, the technic here described will be used.

CONCLUSIONS

1. A reliable chemical method for the quantification of the relative blood volumes of the two lungs in the rabbit is outlined.

2. This method shows that the rabbit's right lung has a much greater blood volume than the left lung.

3. Absorption atelectasis at once reduces the total blood volume of the affected lung to a considerable degree.

4. Compression atelectasis also at once markedly reduces the total blood volume of the affected lung, in a number of instances to an extent far greater than is obtained in absorption atelectasis.

A REVIEW OF UROLOGIC SURGERY

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KIDNEY

Calculi—Ainsworth-Davis¹ reported a case of renal calculus associated with solitary cyst of the left kidney. A man, aged 54, was seen two hours after the beginning of a typical attack of renal and ureteral colic. From four to six years before, he had had attacks of pain in the lower left side of the abdomen, which occurred suddenly and generally lasted from six to seven hours. He had been free from attacks for the preceding two years. Hematuria was noted during a less severe attack.

Cystoscopic examination disclosed mild cystitis and slight swelling of the left ureteral orifice. A catheter was passed to the pelvis of the left kidney. Resistance was noted at the ureteropelvic juncture and about 7.5 cm lower. As soon as the catheter reached the pelvis of the kidney, a flow of urine was established and the renal colic subsided. The roentgenogram did not obtain a shadow indicating a stone in the left kidney or ureter. There was displacement of the renal shadow upward by a spherical body about 10 cm in diameter, which was probably attached to the lower pole of the kidney and moved with it on respiration, this body displaced the lower part of the ureter inward and forward, causing marked kinking. At operation a stone about 1.9 cm long and 1.2 cm wide was found in the renal pelvis. The lower half was replaced by a solitary cyst.

The pain subsided immediately on relief of distention of the renal pelvis, but no relationship was found between the occurrence of the stone

¹ Ainsworth-Davis J C. Renal Calculus Associated with a Solitary Cyst of the Left Kidney, Brit M J 1 10 (Jan 4) 1930

and the cyst Ainsworth-Davis stated that in the case of doubtful renal swelling, exploration should always be done, as an exact diagnosis was impossible in some cases. Renal tumors may reach a considerable size without being palpable if the patient is fat.

Pedroso² performed nephrectomy for tuberculosis and found the renal pelvis filled with soft calculi. Calculi composed of bacteria and fibrin of the urinary tract have rarely been observed. The first observation was made by Marcet in 1817 or 1818, since then 25 cases have been reported. As this condition does not produce special symptoms, the diagnosis has never been made prior to operation, in the majority of cases, calculi have been discovered in operations for other conditions. These calculi, as in the case of hard calculi, may be found in any part of the urinary tract. In most cases reported, they have been present in the kidney, and in a few cases in the bladder. As many as 100 concretions have been found in the kidney by Gage and Beal, 70 were found in Pedroso's case. Fewer are found in the bladder, generally two or three, and they are usually larger. Those of the kidney vary from 1 to 4 cm. in diameter, when numerous they are faceted and have the appearance of gallstones. The color depends on their composition, when they are formed of concentric layers of fibrin and albumin they are yellowish or grayish white, those whose interior is of a granular or pulpy dark-brown substance are brownish white, the color of the contents showing through the capsule. Their consistence is that of wax or of a baked bean, they are elastic and slight pressure crushes them. Examination of the calculi has shown that they are composed of albumin fibrin, amyloid substances and many bacteria. These albuminous substances form concentric layers like the layers of an onion, among which bacterial masses are grouped, in other cases the nucleus is formed by bacterial masses or by mucous filaments. These calculi are formed in the kidneys in pyelitis or pyonephrosis by bacterial nuclei which grow in the periphery and gradually increase in size, by blood clots or necrotic filaments loosened from the renal pelvis in cases of pyelitis, or by pus in pyonephrosis. These coagulations constitute a nutritive medium for bacteria and after having been largely absorbed by them, constitute the albuminous framework of the calculi.

This condition does not cause peculiar symptoms, patients suffering from it complain of symptoms similar to those of renal lithiasis with its complications. The treatment in cases in which there is parenchymatous destruction or pyonephrosis is nephrectomy, if a preoperative diagnosis can be made and there is no parenchymatous destruction, pyelotomy may permit the extraction of the calculi without removal of the kidney.

2 Pedroso Gonzalo. Albumin and Fibrin Calculi of the Kidney, *J. Urol.* 23: 627 (June) 1930.

Koll³ stated that multiple calculi in any part of the kidney, as well as pelvic stones, should be removed. When a single small calculus in a calix is not producing any symptoms it should be left alone. If bilateral calculi are removed, sufficient time for complete convalescence should elapse before the second kidney is operated on. If the opposite ureter contains a concretion, the ureteral calculus should be permitted to pass either spontaneously or by the aid of oil before the renal stones are removed. If there is doubt as to the advisability of nephrectomy, the kidney should be given a chance to recover, as it can always be removed later. Koll does not believe in pyelotomy as a routine procedure. Combined pyelonephrotomy or nephrotomy alone often is productive of less trauma and less permanent ill results. Ninety-eight per cent of calculi that have entered the ureter will pass either spontaneously or with the aid of instrumentation. Cutting into a ureter is not advocated, as stricture results in most instances, necessitating nephrectomy.

Bugbee⁴ considered the large, branching type of calculus and the possibility of its remaining in place for a long time without causing symptoms and not being detected until infection takes place. If watched for a period of years these stones seem to change little and the patients get on fairly comfortably. He cited one instance in which a roentgenogram revealed a stone of this type. After three years the roentgenogram showed that the same calculi were present and were the same size as in the previous roentgenogram. The patient is leading an active life and apparently is in good health.

Pennock⁵ considered the type of microscopic stone that is responsible for hematuria. These cases of essential hematuria have presented an enigmatic problem. Bauer was able to demonstrate small calculi in many cases after much difficulty and the study of numerous sections. He demonstrated minute calculi which he believed were the etiologic factor in a case regarded as essential hematuria in which the kidney was removed because of persisting bleeding which produced secondary anemia. The kidney was apparently normal. Repeated sections gave normal results. One hundred twenty-five sections of the kidney were made before microscopic calculi were found which were believed to be the etiologic factor in the hematuria. He later proved the presence of calculi in several other cases.

Cysts—Hepler⁶ stated that large, usually solitary, cysts of the kidney are acquired. They are not a distinct entity with a common

³ Koll, I. S. Conservatism in Urology. *J. Urol.* **23**: 581 (May) 1930.

⁴ Bugbee, H. G., in discussion of Lewis, B., and Grayson, C. *I. Urol.* **23**: 13 (Jan.) 1930.

⁵ Pennock, W. J., in discussion of Lewis and Grayson (footnote 4).

⁶ Hepler, A. B. Solitary Cysts of the Kidney. *Surg. Gynec. Obst.* **50**: 668 (April) 1930.

etiology Recognized pathologic conditions of the kidney cause them, but only when so situated as to produce a combination of group tubular obstruction and anemic degeneration of the parenchyma from circulatory disturbances in the same segment of the kidney In some instances an additional factor is repeated, prolonged hemorrhages into the same area This conception explains the variation in size, number, contents, wall of the cyst and associated renal conditions on the basis of variation of the direct etiologic factor, the amount of group tubular obstruction and the area of nutritional disturbance depending on the size and distribution of the vessels involved Among the clinical and pathologic features of large renal cysts which lend support to this hypothesis are

1 The average age of 45 years, a period when vascular lesions, such as arteriosclerosis, endarteritis, aneurysms, infarcts and acquired lesions, such as tumor, are common

2 The rather frequent association of these cysts with lesions which might produce the conditions assumed to be necessary for their formation

3 The presence of groups of atrophied glomeruli and tubules in the wall of the sac, indicating its origin from renal parenchyma which has undergone compression atrophy with substitution by connective tissue

4 The presence of remnants of neoplasm in the walls of many of the hemorrhagic cysts as the only indication that a tumor was concerned with their formation

Finally, by creating experimentally the conditions assumed to be necessary for the formation of cysts Hepler stated that he was able to reproduce a large solitary cyst similar in every detail to those found in the kidney of man

Grove⁷ stated that in most of the reported cases of solitary serous cysts of the kidney, urinary symptoms, if present, were slight Attention is drawn to the genito-urinary tract by the presence of a palpable mass in the abdomen, or as a result of exclusion of the kidney as a source of the lesion As these cysts do not communicate with the calices or renal pelvis, pyelograms usually do not show distortion of the pelvis unless the cyst is large enough to bulge into it If the cyst is at the upper pole, it may, by its weight, push the kidney down, producing ectopia Displacement of the kidney may produce various deformities of the ureter which may cause symptoms referable to the urinary tract

Grove reported a case of solitary cyst of the kidney which was large enough to produce symptoms of pressure referable to the gastro-intestinal tract Functional and cystoscopic studies did not reveal anything abnormal Although the cyst was large, it was possible to perform a partial resection and save a large portion of a normally functioning kidney Such tumors are not uncommon, as noted by pathologists

⁷ Grove, J S Solitary Serous Cysts of the Kidney, *J Urol* 23 661 (June) 1930

Polycystic disease of the kidney is extremely uncommon in children. Wakeley⁸ noted the rarity of unilateral occurrence. He reported the case of a boy, aged 20 months, seen on April 6, 1929, with a large abdominal tumor, which was first noticed by the child's mother a few months after birth. The child was the third of the family, the other children were normal. Examination revealed a large, smooth tumor which occupied the whole right side of the abdomen and extended up toward the margin of the liver and across the median line. The tumor was firm and felt like rubber. The urine was normal except for a few erythrocytes and pus cells. Renal function was normal. Nephrectomy was performed on April 22 through an anterior incision, with removal of the large tumor. The opposite kidney was examined and found to be apparently normal. Convalescence was uneventful, the child gained rapidly and left the hospital on May 5. When he was last examined the disease had not developed in the opposite side.

The tumor measured about 18 by 12 cm. and weighed 1.6 Kg. It was reniform with definite cystic dilatations on its surface. The pelvis of the kidney was definitely dilated. On section, normal renal tissue could not be seen. The kidney contained numerous cystic spaces varying considerably in size. Some of these spaces contained fluid, others contained a colloid substance. The structure of the kidney had been completely replaced by the cysts. The type of epithelium lining the cysts showed considerable variation, in some it was definitely columnar, with large vesicular nuclei situated toward the base of the cells. In other cysts, including the smallest, the epithelium was flattened and the cells resembled endothelial cells. All intermediate types of cell were present. In all cysts the epithelium was only as thick as a single cell. The stroma was loose and fibrous, showing areas of hyaline degeneration. Hemorrhage, mostly recent, had occurred. Some pigment was present chiefly within phagocytes. The stroma also showed areas of infiltration with inflammatory cells including large numbers of plasma cells.

Hydatid Disease—Lee-Brown⁹ stated that the diagnosis of a renal hydatid depends on the physical signs and symptoms, the chief of which is the presence of tumor. If the cysts rupture, with absorption of a considerable amount of antigen general symptoms of hydatid anaphylaxis may be present. The condition of the urine depends on whether the hydatid is open or closed. In the closed variety hematuria may occur only occasionally. In the open type with infection superimposed hooklets, scolices, small daughter cysts and pieces of laminated membrane may be found. Pelvegraphic evidence is of special significance.

8 Wakeley C. P. G. A Case of Unilateral Polycystic Kidney in a Child. *Brit. J. Surg.* **18**: 162 (July) 1930.

9 Lee-Brown R. K. Renal Hydatid Disease. *J. Urol.* **23**: 611 (June) 1930.

In long-standing cases deposition of lime salts often occurs in the thickened adventitia. This deposit of calcium renders the adventitia impervious to roentgen rays and casts a characteristic shadow. Such calcification occurs only occasionally and cannot be expected in every case. Roentgenograms do not offer much diagnostic aid early in the disease, but the pyelogram, except in a small percentage of cases, supplies evidence, depending on whether the hydatid is open or closed. In the event of closed hydatid, the evidence produced will be similar to that of a localized tumor obliterating a portion of the pelvis.

The treatment for hydatid disease in general is essentially surgical. There is no direct blood supply to a hydatid cyst and it depends entirely on osmosis for its nutrition. The earliest surgical treatment was the aspiration method, consisting of the introduction of a hollow needle into the cyst and withdrawal of the fluid. By this method it was hoped that collapse of the cyst would occur and be followed by fibrous degeneration. The operation failed to produce the desired results, and complications frequently resulted which called for more radical measures. Puncture of the cyst often permitted escape of hydatid fluid into the surrounding tissues, and in this way scolices escaped and later developed into secondary daughter cysts. If much fluid escaped there was grave danger that anaphylactic shock might result. Infection often resulted from puncture of the cyst in spite of rigid aseptic technic, and frequently incision and drainage were necessary. The surgical measures now employed depend on whether the disease is confined entirely to the kidney or whether it extends beyond the kidney into the adjoining tissues. Nephrectomy is the operation of choice in all cases of renal hydatid and in the majority of "closed" cases. There are two exceptions to nephrectomy in closed cases of hydatid disease: (1) if the cyst is small and confined to one pole of the kidney, partial nephrectomy might be considered, and (2) if the cyst is calcified, which means activity has ceased and the remaining renal tissue is worth conserving, there is no object in surgical removal. If there is one large simple and adherent mother cyst, in which gross infection is not present, it is exposed through the loin and after careful packing off, a trocar attached to a suction apparatus is introduced and the fluid content withdrawn. Following this, alcohol or a solution of formaldehyde (10 per cent) is introduced, slightly less in quantity than the amount of hydatid fluid withdrawn. This is left in place for three or four minutes in order to devitalize the parasite. The alcohol or formaldehyde is then withdrawn, the cyst is incised and the content, consisting of daughter cysts, laminated membrane, brood capsules and debris, is removed. The cyst having been completely emptied the interior is swabbed out with alcohol, the cyst is closed with catgut sutures and the collapsed wall is sewed to the deep aspect of the lumbar incision. A rubber tissue drain is introduced down to but not into the cyst and the

wound is closed in the ordinary way. The rubber tissue drain is employed because of the effusion that invariably follows evacuation of the cyst.

Ectopy—Campbell¹⁰ reported a series of 27 cases of renal ectopy observed in 13,000 postmortem examinations, with a brief consideration of the anatomico-clinical features of ectopy. The condition occurred once in about 660 cases. The anomaly is sufficiently common and is so potentially serious clinically as to warrant grave consideration. The technical difficulties of surgical intervention are usually extreme in the treatment of low ectopic kidneys, and are due not only to the site of the organ but to the congenitally short ureter and short, anomalous vascular supply. If a seriously diseased kidney is low in the pelvis and the remaining kidney is functionally competent, nephrectomy is the treatment indicated since it is anatomically difficult or impossible to accomplish extraperitoneal drainage of these organs, and transperitoneal drainage usually results in peritonitis. In none of Campbell's series was renal ectopy a direct cause of death.

[Ed. Note—Campbell, in 1929, reviewed fifty-five cases of rupture of the bladder from the Bellevue Hospital. His conclusions in general agree with those of de Tarnowsky. The diagnosis of rupture of the bladder is not always simple. Shock is common. Pain in the lower part of the abdomen, withdrawal of a variable amount of blood-stained urine by catheter (often more confusing than helpful), cystoscopy, pneumocystography or air cystography may help in diagnosis. A history of trauma with an overdistended bladder and the inability of the patient to void, except in small amount at times and with strangury are salient features in the picture. Evidence of peritonitis or peritoneal irritation when the rupture is intraperitoneal and the finding of pre-vesical, perivesical, perinectal or subcutaneous urinary extravasation in the abdominal wall or pneumoperitoneum are of diagnostic import. From a survey of case reports it is easy to understand why it is often difficult to avoid delay in proper surgical treatment.]

Rupture of the bladder is almost always associated with trauma, it is a frequent occurrence with alcoholism, at times with preexisting vesical disease, but probably is rare with simple distention. The condition is often accompanied by other traumatic lesions such as rupture of the spleen, liver or kidneys or by fracture of the pelvis.

Immediate operation is indicated. If possible, the rupture should be exposed and sutured. Campbell advised suprapubic drainage of the bladder with a large rubber tube. Prevesical or culdesac drainage or the use of the catheter à demeure as recommended by de Tarnowsky are considered by Campbell as inferior to suprapubic cystostomy. The

¹⁰ Campbell M. F. Renal Ectopy. *J. Urol.* 24:187 (Aug.) 1930.

condition is to be regarded as an emergency, as each hour of delay brings a risk of increased mortality. Twenty of the fifty-five patients reported by Campbell as having recovered were all operated on. Both authors urged that when the diagnosis of vesical rupture is established or strongly suspected, abdominal exploration be made as an emergency procedure.]

Deming¹¹ studied fifty-five cases of nephroptosis. The excursion of the kidneys varied from 4 to 12 cm., the average being 5.5 cm. In 51 per cent of the cases ptosis occurred in the right kidney, in 11 per cent in the left kidney and in 19 per cent it was bilateral, in 7 per cent of the cases general visceroptosis was present. Twenty per cent of the kidneys were rotated through one or more planes up to 180 degrees. This observation, Deming stated, is important in correcting the position of the kidney at operation. The function of the ptotic kidney is rarely modified. Thirty-three per cent of the kidneys were infected with *Bacillus coli*, most of the pelves which were infected had a slight increase in capacity, although only 7 per cent had more than 20 cc., 66 per cent had a normal pelvic capacity. In all of the cases kink, stricture or tortuosity of the ureter was present, in 80 per cent kinks were found, in 50 per cent tortuosity and in 13 per cent stricture. Deming noted the symptoms of the ptotic kidney as mainly pain, acute and chronic, due mostly to obstruction of the ureter.

In performing nephropexy, Deming begins the incision high in the costovertebral angle, continuing it downward and transversely across, halfway between the lower rib and crest of the ilium, incising portions of the external and internal oblique muscles in most cases. Approach to the kidney is made through the triangle of Petit. The fatty capsule is opened, and the kidney which is usually low-lying is easily recognized. The hand is inserted under the liver to the diaphragm. The kidney can then be replaced sufficiently high to remove all kinks and most of the tortuosities of the ureter. A series of interrupted chromic mattress sutures no. 0 are then placed through the perirenal fascia and peritoneum to the quadratus muscle. From five to eight sutures are necessary to close this aperture, they form a basket-sling for the kidney so that it is impossible for the organ to descend. This row of sutures is now enforced by bringing up all the extraperitoneal fat and suturing it with two or three mattress sutures to the quadratus muscle below the other line of sutures. The patient is kept flat in bed for sixteen days, allowed out of bed on the eighteenth day and home on the twenty-first or twenty-second day. None of the patients had complications and all but one were completely relieved of the symptoms.

11 Deming, C. L. Nephroptosis. Its Relation to the Liver, Spleen, Stomach and Its Correction by Means of a New Operation, *Am J Surg* 9:218 (Aug) 1930.

Hydronephrosis—Legueu and Fey¹² stated that distention of the renal cavities, the characteristic lesion of hydronephrosis is the result of two agents, dilatation and retention. Dilatation is an anatomic lesion of a static and steady nature. Retention is a physiopathologic lesion and arises from poorly performed functions of the pyelo-ureteral muscle. Although an evident anatomic lesion is found, one must make certain before admitting its pathogenic action, that it is a first cause of retention and not a secondary deformation connected with the developments of the dilatation. Certain aspects of pyelography and ureterography favor the mechanical theory. It is necessary to ascertain definitely that these deformations are permanent and do not correspond to normal and physiologic contractions. Observation by pyeloscopy in the majority of cases demonstrates that there is neither arrest nor delay of the evacuation of the opaque medium. Hydronephrosis from mechanical reasons seems uncommon and can hardly be accepted except in cases in which catheterization is impossible. The congenital theory would be a structural abnormality, incompetence of the pyelo-ureteral muscle. There are some unquestionable cases of hydronephrosis those in which the renal apparatus discloses morphologic malformation but it is difficult to place in this group the majority of cases of pelvic retention. The existence of functional retention is proved by the many cases in which there is retention without any congenital lesion or mechanical obstacle. Such is the case with slight hydronephrosis characterized by retention without dilatation. This functional retention is connected with impaired action of the excretory apparatus, the variations of which can be studied by physiology and pyeloscopy. Certain experimental and clinical operative facts tend to substantiate this theory. Excretion is assured by the functional synergy of several muscular actions, which are pelvic contractions culminating in the formation of a bulb, a pyelo-ureteral sphincter action that controls the filling and evacuation of the ureter, peristaltic contraction of the ureter, a ureterovesical sphincter action that protects the ureter against the back pressure in the bladder during urination.

Clinical diagnosis depends on the character of renal pain. The most typical pain is renal colic connected with a spasm of the pelvic musculature entailing a crisis of acute retention. The diagnosis can be made only after complete roentgenologic examination.

Operative treatment is based on the pain, on the presence of infection, on the dilatation and on the degree of chronic retention. If operation is decided on, some improvement is obtained by catheterization of the ureter. If operation is performed, Legueu and Fey carefully look for causes that provoke the phenomena of excitation and inhibition.

¹² Legueu, F. and Fey, B. Hydronephrosis. *Brit J Urol* **2** 131 (June) 1930.

disturbing excretion Nephrectomy is performed exceptionally, keeping in mind the volume of the sac, its infection, the condition of the remaining parenchyma, and the tonicity and activity of the calices and ureter which are explored in the course of the intervention In other cases two eventualities occur If it is possible to determine the lesion causing the retention, this cause is removed, no complementary procedures being used, if it is not possible to determine the cause of the retention, nephropexy, renal intervention or temporary nephrostomy is performed

Eisendrath¹³ reported a case in which the obstruction of the renal pelvis was due to the lower of 2 main renal arteries Although cases of obstruction of the renal pelvis by branches of a main renal artery have been reported, Eisendrath's case is the first to be reported of obstruction by 1 of 2 main renal arteries He advised against ligation of a polar artery, because of the danger of necrosis of the area supplied by such a vessel, the same being true of ligation of 1 of 2 main renal arteries The frequency of the variations of the renal vessels which are of clinical importance was reviewed Lower polar arteries from the aorta were found in 5 per cent of 1,337 kidneys, and 2 main renal arteries were found in 11.2 per cent of 1,319 kidneys by various observers Abnormal mobility of the kidney, as pointed out by Mathé, plays the most important part in favoring obstruction by a polar artery or by 1 of 2 main renal arteries

Walters¹⁴ stated that the causes of hydronephrosis consist for the most part of anomalous blood vessels, usually an artery and a vein which cross and change the angle of ureteropelvic drainage, with the possible interference of ureteral peristalsis by pulsation Unless search is made for these vessels as they cross the ureteropelvic juncture, they are easily overlooked With these vessels, it is usually found that angulation of the ureter at the ureteropelvic juncture by the renal pelvis or perirenal pelvic connective tissue has occurred which, with dilatation of the renal pelvis, produces ureteral compression In some cases the absence of demonstrable obstruction in the presence of large hydronephrotic sacs suggests disturbances of neuromuscular control of the renal pelvis and upper part of the ureter If an anomalous vessel is compressing the ureter at the ureteropelvic juncture, thus changing its course and interfering with proper emptying of the pelvis, and if the additional blood supply is sufficient, the anomalous vessel should be divided If, however, as a result of this type of obstruction, the extrarenal pelvis is considerably dilated, it is resected to within 1.5 cm of

13 Eisendrath D N Hydronephrosis Due to Obstruction of the Renal Pelvis by One of Two Main Renal Arteries *J Urol* **24** 173 (Aug) 1930

14 Walters, Waltman Resection of the Renal Pelvis for Hydronephrosis Its Complications and Results, *Surg Gynec Obst* **51** 711 (Nov) 1930

the renal substance, leaving the ureter attached to its dependent portion. Closure of this opening in the pelvis removes the hydronephrotic sac and changes the course of the ureter, and its opening becomes dependent. In the cases in which this was done, nephropexy was also performed to prevent further ureteral angulation. In some cases temporary nephrostomy was done also, to relieve pressure on the suture line. If for any reason there is a question of inadequate blood supply from the remaining vessels to the kidney, circulation in the anomalous vessels should not be obstructed, particularly if the opposite kidney shows any abnormality of function. Such obstruction existed in one case in which there was a large hydronephrotic sac on both sides. In such cases the dilated extrarenal pelvis is resected, or the ureter is reimplanted into the dependent portion of the pelvis away from the anomalous vessels. In several cases of hydronephrosis in which nephrectomy was necessary because the kidney was largely destroyed, compression, angulation and obstruction of the ureteropelvic juncture occurred as a result of a dense sheath of connective tissue.

Resection of the hydronephrotic renal pelvis was done in one case in which there was no demonstrable cause for the obstruction. The dilated portion of the left hydronephrotic pelvis was excised and the ureter was severed from the pelvis and reimplanted into its dependent portion. Removal of the ureter from its lateral attachment to the hydronephrotic renal pelvis and its reinsertion by suture to the dependent portion of the pelvis away from these anomalous vessels is indicated if the anomalous vessels crossing the ureteropelvic juncture are of such size and importance that their division and ligation seem inadvisable.

Walters expressed the opinion that postoperative complications center around (1) leakage of urine at the point of anastomosis with perirenal accumulation, (2) retention of urine in the kidney, leading to pyelonephritis or cortical abscesses in the kidney, and (3) ureteral obstruction at or below the pelvic incision with a persisting urinary fistula from the pelvic anastomosis. In eleven cases of hydronephrosis resection of the renal pelvis was performed. In eight cases (nine resections) the results of operation were excellent. In four of these cases hydronephrosis was bilateral, and the renal pelvis was large and infected. Bilateral resection was performed in one case. In three additional cases of bilateral hydronephrosis successful resection of one hydronephrotic renal pelvis was performed. In three cases in which resection of the renal pelvis was performed secondary nephrectomy was required due to (1) persistent urinary fistula from occlusion of the ureter by postoperative infection around the ureter and (2) pyelonephritis with cortical abscesses in two cases in which urine was being transmitted successfully from the resected renal pelvis to the bladder through the ureter. Complete recovery followed nephrectomy.

Covisa¹⁵ divided hydronephrosis into two main groups that due to causes of a mechanical nature and that due to causes of a dynamic nature. Among the causes of a mechanical order are included all organic lesions, congenital or acquired, such as tumors, inflammatory processes, foreign bodies, narrowness, bends and valvular formations which acting either from inside or from outside of any part of the urinary tract place difficulties in the way of normal excretion of urine. Under dynamic hydronephrosis may be grouped all cases in which no appreciable organic cause exists to which the development of hydronephrosis can be attributed. Its causes are sometimes processes of a toxic infection, of inflammatory infiltration of the walls of the ureter, or of disturbances of the nervous system. Modern pyeloscopic explorations and the experimental work of many investigators have demonstrated that peristalsis of the pelvi-ureteral muscle can be modified by motor disturbance and by disturbance of tonus. Motor disturbances can be excessive or defective. If excessive, they produce a hyperknetic syndrome characterized pyeloscopically by a more rapid emptying of the pelvis than normal. They give rise to an incomplete retention syndrome which is revealed pyeloscopically by retarded evacuation. These motor changes are manifested clinically by painful spasmodic crises, and are characterized by the absence of dilatation of the pelvis.

The treatment for hydronephrosis can be either radical or conservative. The radical treatment is nephrectomy, the conservative is nephrostomy, pyelotomy, nephropexy, denervation of the renal pedicle, cutting of the aberrant vessels and various plastic operations. Whenever conservative treatment is possible it should be used. In many cases conservative plastic operations should be combined to bring about a more perfect therapeutic action, in all cases complementary nephropexy should be practiced to correct the mobility of the kidney caused by the measures employed for isolating and bringing it to the surface.

[ED. NOTE.—The present tendency of urologic surgeons is to employ the most conservative methods in the treatment for renal lesions whenever such measures are compatible with satisfactory results. It is now possible to utilize the less radical procedures, with the consequent saving of functioning renal tissue, sufficient in some instances to support life. These procedures are especially applicable in lesions such as bilateral hydronephrosis. White in a study of hydronephrosis, found that the commonest form of the disease was that in which the dilatation of the kidneys began at the ureteropelvic junction. In a large proportion of his cases, which were identified in early life and which were undoubtedly congenital the disease was bilateral. Usually the first manifestations

15 Covisa, I. S. Etiology and Treatment of Hydronephrosis. *Brit. J. Urol.* 2: 133 (June) 1930.

are in adult life. The earliest cases show narrowing of the ureter from chronic inflammation, which appears to be the cause of the dilatation. In all cases pyelitis and moderate chronic interstitial nephritis are associated. Papin stated that in the surgical treatment for hydronephrosis two extremes should be avoided: the essentially surgical and the radical. Nephropexy serves satisfactorily if the ureter is kinked and is unsatisfactory in cases in which small congenital dilatations are present. Meier concluded from his experience with the etiology and treatment of hydronephrosis that most cases are produced by pelvic or ureteral membranes and by lowering of the kidney from 1 to 2 cm. from some undetermined cause. He stated his belief that nephropexy is the logical operation for some types of hydronephrosis because it reestablishes the normal position of the pelvis toward the ureter. Marion obtained good results in treating a number of patients for hydronephrosis by liberating the ureter at its superior position and fixing the kidney as high as possible. He stated that some cases are not due to narrowing of the ureter, but to extreme fixity to the surrounding cellular tissue and to slight ptosis of the kidney.]

Pyelovenous Backflow—Fuchs¹⁶ reported on pyelovenous backflow. If one injects fluid into the ureter of a human being or into the kidney of an animal after removal, the fluid often flows out by way of the renal veins because of a direct connection between the vascular system and the upper portion of the renal pelvis. An attempt to establish the practical significance of this phenomenon has been made through animal experiments. The exact part that the pyelovenous backflow plays in pathologic changes in man is the specific object of Fuchs' paper.

A short survey of the literature, from the first observations of Gidon (1856) up to the present was given. Some of the more important points regarding pyelovenous backflow given by different authors were considered. Among these were:

- 1 The fate of fluid forced under pressure into the renal pelvis through the ureter. Experimental evidence has shown that such fluid is found in all tissue elements of the kidneys chiefly in the lymph spaces and blood vessels, especially in the veins, and least in the uriniferous tubules.

- 2 The mechanism of the passage of fluid from the renal pelvis into the veins, as well as into the lymph vessels and uriniferous tubules. Summing up the experimental and anatomic data, it may be said that pyelovenous backflow is accomplished by direct communication between the pelvis and the venous system initiated by rupture of the renal pelvis.

- 3 The pressure necessary to produce pyelovenous backflow. According to all investigators this pressure is exceptionally small. No difference was found in the required pressure of kidneys of cadaverous and living animals.

¹⁶ Fuchs, Felix. *Pyelovenöser Reflux und Hydronephrose*, Deutsche Zeitschrift für Chirurg. **224** 353 (June) 1930.

Fuchs also reviewed his investigations on the kidneys of human cadavers. Notwithstanding certain well recognized differences between the intrarenal topography of the kidneys of mammals and of man, there are significant analogies in the pyelovascular mechanism. The place of pyelovenous backflow is at the apex of a minor calix, called the fornix calices in the kidney of man. Fuchs has shown by means of a macerated preparation the relation between the fornix calices and the venous plexus of the renal sinus. He found three fourths of the circumference of the fornix calices often surrounded by a venous plexus. It is thus clear that the venous circulation in the calix must sustain considerable injury in the event of expansion of the calix. The renal pelvis is regarded as the strongest ductile segment of the upper urinary passages, whereas the parenchyma of the kidney lacks extensive ductility. It is apparent that the line of separation between the weak and strong parts of the pelvic cavity is at the point of insertion of the calix in the parenchyma of the kidney, namely, at the fornix calices. This is the place of predilection for rupture in internal pressure. For the purpose of observing the conditions of rupture of the venous system from injected fluid Fuchs injected a 20 per cent solution of sodium bromide into normal kidneys of human cadavers of different ages, as fresh as possible. The injections were watched fluoroscopically. The passage of the fluid from the pelvis into the venous channels was accurately noted. The same phenomenon was studied by means of the corrosion method, in which celluloid dissolved in acetone was injected into the ureter until the mass appeared at the stump of the renal vein. By this method it was shown that the veins were filled by extravasation from the fornices calices. In spite of these observations, it was not clear whether the fluid that left the pelvis at the fornix calices actually entered the surrounding vein stems, and much less clear why this should be the case. Answers to these questions were obtained by further and more minute study of the anatomic relations of the venous system of the kidney. It was found that an artificial perivenous space was created when the veins were forced away from the adjacent renal parenchyma by the extravasated fluid from the ruptured fornix calices. This forceful separation of the vein stem from the parenchyma caused stretching and rupture of the many small venules emerging from the parenchyma to enter the veins. These ruptured venules thus permitted direct communication for the passage of the extravasated fluid from the perivenous spaces into the veins. It is probable that other forms of extravasation, such as subcapsular and sinus hilar extravasations, which are considerably less frequent than pyelovenous backflow, also result from the rupture of small vessels leading to the various types of veins found in close relationship with the renal pelvis. A number of investigators have attributed pyelovenous backflow to direct penetration of the papillary duct openings of the

papillae Fuchs, although unable to demonstrate this himself, admitted its possibility in rare instances and then only at a very high pressure. The pressure at which pyelovenous backflow occurs and whether or not such pressures occur spontaneously are of significance. It is shown that in renal colic there is an increase in intrapelvic pressure of the kidneys and that this pressure is of the same nature and actually exceeds that produced during pyelographic filling of the pelvis. The question is whether these higher pressures cause pyelovenous backflow. There are two ways by which it may be shown when pyelovenous backflow occurs in human beings: direct observation by pyelography and the reaction of the organism to increases in pressure in the renal pelvis due to artificial or spontaneous causes. If pyelographic injections are done carefully they are stopped as soon as the patient complains of pain. The abnormal shadows sometimes seen about the calices in pyelograms represent the initial stages and not the actual pyelovenous backflow as studied experimentally. Of more practical significance is the greater pressure produced in the renal pelvis during attacks of colic. In such attacks symptoms of injection are common. Fuchs stated: "The septic fever curve in the temperature course of patients with congestion and infection of the urinary passages should always be considered as the clinical expression of pyelovenous backflow waves." Attention is called to the fact that rupture of veins occurring in pyelovenous backflow may be the source of hemorrhage in such conditions as intermittent hydronephrosis and colic associated with pelvic or ureteral calculi. It is possible that pyelovenous backflow may open the way for ascending infections of the parenchyma of the kidney.

Surgical Complications—Schwarz¹⁷ stated that renal complications are among the relatively rare but clinically important sequelae of operations. The four basic forms may be differentiated: (1) disturbances in function, (2) inflammatory, noninfectious diseases, (3) infectious diseases and (4) the effects of changes in the efferent urinary passages of the kidney. Postoperative disturbances of the function of the kidney are transient, but may also lead to death. They may be produced by inhibitory reflexes which originate in the other kidney or in the bladder. In some of the cases in which the postoperative fatality is sometimes attributed to the shock of the operation, the cause is masked uremia, for this reason, a test of renal function is always made before every major operation. Postoperative, inflammatory noninfectious diseases of the kidney in the form of simple degeneration, nephrosis or even nephritis are usually attributed to the anesthesia but in general it may be said that the effect of the anesthesia, especially since chloroform is no longer in common use, is markedly overestimated.

17 Schwarz, Oswald. Postoperative Kidney Complications. *Am J Surg* 8: 1206 (June) 1930.

The infectious diseases of the kidney, owing to the frequency of their occurrence, demand by far the greatest amount of consideration. Urethritis, cystitis, ureteritis, pyelitis, pyelonephritis, abscess of the kidney and pyonephrosis are merely different localizations and, under certain conditions, different stages of the same disease process. One sees cases in which the entire urinary tract is actually attacked by the infection. Formerly the colon bacillus was almost exclusively blamed (90 per cent of the cases) as the exciting germ, but more recent investigations have shown that cocci of various types are constantly gaining greater significance in the hematogenic infections, and particularly in the sequelae of operative interventions.

Schwaiz expressed the opinion that the indispensable prerequisite for infection of the pelvis of the kidney is motor insufficiency with or without dilatation of the calyx-renal-ureter tubule, also that the diagnosis of "chronic pyelitis" as an independent disease picture is always wrong. He stated that the chronic suppuration originating in the pelvis of the kidney is never an independent disease, but always merely a symptom and that the aim of the diagnosis is to determine what the factors are that prevent this tendency to spontaneous healing of the inflammation and favor chronicity. Two pathologic factors enter into consideration at this point: the dilatation of the renal pelvis mentioned and the infection of the renal tissue itself. Schwaiz expressed the belief that infected residual urine in the pelvis of the kidney is the primary cause of the chronicity of renal pyuria, the second cause is the pyelonephritis. He further stated that every urologic disease having its onset with severe clinical symptoms, including a high temperature and chill, is due either to a metastatic infection of previously formed hydronephrosis or, in most cases, to the development of metastatic cortical abscess in the kidney. As infections of the kidney following surgical intervention are almost always hematogenic-metastatic, one may say that embolic pyelonephritis represents the typical postoperative complication as far as the kidneys are concerned. The sources of the infection are: the infected urinary bladder, from which the kidney may be infected by both an ascending and a metastatic route; every pus focus anywhere in the body and finally the intestinal tract.

Severe disease of the kidney may develop under unfavorable conditions from even the most harmless appearing postoperative bacteriuria or mild pyuria. According to Schwaiz' view, careful control of intestinal motility occupies the center of the stage in all prevention and treatment of infections of the urinary tract from the colon bacillus.

Tuberculosis—Braasch¹⁸ considered some of the problems that have arisen recently in the diagnosis and treatment of renal tuberculosis.

18 Braasch, W. F. Tuberculosis of the Kidney, *J. Urol.* 23: 669 (June) 1930.

Among the common sources of error in the diagnosis of this disease are confusion of roentgen shadows caused by lithiasis with calcified processes of tuberculosis, failure of clinical differentiation of pyelonephritis and tuberculosis, overlooking tuberculosis as the primary cause in some cases of hydronephrosis, confusion of granuloma in the bladder secondary to tuberculosis with malignant tumor, failure to appreciate the significance of slight pyuria which may occur without any other clinical evidence in early renal tuberculosis, and the incorrect interpretation of the results of inoculation of guinea-pigs.

Probably the most refined test available in the diagnosis of renal tuberculosis is inoculation of guinea-pigs. Cases have been reported with positive results from the inoculation of guinea-pigs with the urine from supposedly normal kidneys. In 1924, Scholl and Braasch reviewed the records of a small group of patients who had been operated on for supposed unilateral renal tuberculosis and inoculations of guinea-pigs with urine collected from both kidneys had been made. A positive report concerning the supposedly well kidney had been obtained in a number of cases and it was inferred that many of these patients might have had bilateral tuberculosis. Several years later tests were done in 109 cases, including the 18 or 20 previously studied. Although the inoculation of guinea-pigs made with the urine from the supposedly normal kidney again gave positive results in many cases, it was found that most of the patients were alive and well three or more years after operation and that many of them gave negative results on urinalysis. It was evident that the positive reports from the normal kidney were caused by regurgitation of the bacillus of tuberculosis from the bladder into the atonic lower portion of the ureter on the normal side. After nephrectomy the bacillus persists in the urine from the bladder and regurgitates into the normal ureter for a considerable length of time. Cases have been observed in which a tuberculous kidney was removed and five years later inoculation of guinea-pigs with the urine from the remaining kidney, which was otherwise normal, gave positive results. The value of the differential renal functional test is another factor in diagnosis emphasized by certain observers. It has been claimed that a definite lesion could not be present in the kidney without causing retardation and diminution of the return of indigo carmine (sodium indigotin-disulphonas). It has been Braasch's experience with a divided functional test that although it is often of diagnostic value, there are so many factors involved in the excretion of the dye—the time of appearance and the intensity of color—that the test is frequently inexact and misleading. It is not unusual for the secretion of phenolsulphonphthalein or methylene blue (methylthionine chloride, U.S.P.) to be retarded fifteen or twenty minutes on both sides in spite of the fact that the blood urea is normal.

It has been stated recently that American urologists use urography too much in diagnosis, particularly in renal tuberculosis. It has also been said that urography is seldom necessary to diagnosis and that it is dangerous when employed in renal tuberculosis. In the hundreds of cases of renal tuberculosis observed at the Mayo Clinic in which urography was employed, no serious harm was done. Urography may prove to be the only means of arriving at a positive diagnosis in the presence of the following conditions: (1) early lesions and small circumscribed areas, (2) tuberculosis confined to one kidney and positive results from the inoculation of guinea-pigs with the urine of the other kidney, (3) differentiation of ureterectasis that is secondary to ascending ureteritis and that occurring with pyelonephritis, (4) identification of doubtful renal shadows, (5) differentiation of pyelonephritis and tuberculosis and (6) determination of the cause of a few pus cells recovered from the supposedly normal kidney. Although occasionally the pelvic outline is normal, it can be stated that a negative pyelogram will exclude tuberculosis in fully 90 per cent of cases.

Although nephrectomy is usually contraindicated in cases of bilateral tuberculosis, it may be considered occasionally if there is excessive pain, hematuria or acute sepsis in one kidney and if the other side is only slightly affected. Although nephrectomy is not advisable without positive indications, the removal of an occluded kidney apparently relieves such symptoms as dull lumbar pain or vesical irritation, and the patient's general condition improves.

Another problem frequently presents itself in the treatment of patients who continue to have dysuria and frequency several years after nephrectomy. Blasch recently reviewed sixty-five cases in which nephrectomy had been performed between five and fifteen years previously. These patients had had advanced secondary ulcerative cystitis with a markedly reduced capacity of the bladder. Within five years after operation there was a mortality of 37 per cent, somewhat higher than the average. When nephrectomy is performed soon after the onset of infection and before the bladder becomes too involved, the results are much better than in cases in which the duration averages five or six years. The fact that 30 per cent of a group of patients with advanced cystitis and contraction recovered shows to what extent the diseased bladder can recuperate.

Reference is made to a syndrome, similar to that of traumatic shock which has been observed in several cases following nephrectomy for renal tuberculosis. In two cases the suprarenal gland was removed with the kidney, and in the other cases it may have been injured. This might explain some of the symptoms, which were suggestive of acute suprarenal insufficiency. The condition was characterized by a sudden drop in blood pressure and extreme prostration, followed by death in

from twenty-four to thirty-six hours. In case the suprarenal gland is removed, steps should be taken to overcome possible insufficiency of epinephrine.

Kretschmer¹⁹ reported 221 cases in which he had observed the patients, 43.5 per cent had had some sort of an operation, 42 of the patients (47.7 per cent) had had an operation for a tuberculous disease. The largest number of cases occurring in any one decade was 73, the ages ranging between 20 and 29. More than half the cases (56 per cent) occurred in patients between 20 and 39 years of age. Kretschmer referred to Wildbolz' report of 245 cases in which bilateral renal tuberculosis was found in 12 per cent of the series, to Brongersma's report of 14 per cent, and to Braasch's 16 bilateral cases in his series of 532 (3 per cent). The records of 180 cases were available, in 35.5 per cent of which there was evidence of involvement of the lungs. Thirty-nine of 123 males had lesions involving the genital tract, that is, of the prostate gland and vesicles, and 26 of these also had lesions of the epididymis. In 121 cases (54.7 per cent) the symptoms had been present for one year. In the next largest number symptoms had been present for two years, there were 33 in this group. Therefore, in 154 cases (69.6 per cent), symptoms had been present for two years before the patients came under observation and were given the correct diagnosis and treatment. Frequency of urination was present in 184 cases (83.2 per cent). Nocturia was present in 166 cases. Pus was present in 201 cases (90.9 per cent). In 194 cases (87.7 per cent) the bacillus of tuberculosis was demonstrated by smear, by inoculation of guinea-pigs, or by both.

Hegedus²⁰ stated that the success of renal decapsulation for curing chronic nephritis, as proposed by Edebohls, has been doubtful but that some good results have been achieved in cases of associated oliguria and anuria in pyelonephritis, of which the following case is an example. A right tuberculous kidney was removed from a youth aged 19 years. Convalescence was uneventful and he was dismissed from observation on the eighteenth day. Three months later he reported diminishing urinary output. Catheterization showed the bladder to be empty. He had moderate fever and no appetite, and he complained of severe headache and nausea. The nonprotein nitrogen content was 41 mg. Examination did not reveal mechanical obstruction of the left ureter. A ureteral catheter was passed into the pelvis and left in place for six hours. The pelvis was lavaged but without success. After anuria for twenty-four hours decapsulation was carried out under intercostal anesthesia.

19 Kretschmer, H. L. Tuberculosis of the Kidney, *Am J Surg* 9:221 (Aug.) 1930.

20 Hegedus, Karl. Nephrektomie wegen rechtsseitiger Nierentuberkulose. *Ztschr f Urol* 23:847 1929.

with procaine hydrochloride. The kidney was twice the normal size its capsule was stretched and it was dark brown and congested. Examination did not reveal a lesion. The patient received 500 cc of a 4 per cent solution of dextrose immediately after the operation. The bladder was catheterized forty-five minutes later, and 30 cc of cloudy urine was obtained. Bacteriologic examination continually revealed pus and colon bacilli. In twelve hours 350 cc of urine was secreted, and the blood pressure dropped to normal. The patient made a good recovery. After the fifth day the output of urine increased to 1,000 cc in twenty-four hours. The bacillus of tuberculosis was not found, and tests on animals were negative. Three weeks after operation indigo carmine appeared on functional test in six minutes and nonprotein nitrogen had dropped to 24.2 mg. Three and a half months after operation the patient was in excellent health and had gained considerable weight. Indigo carmine appeared in four minutes, and nonprotein nitrogen was 25.09 mg.

Crenshaw²¹ stated that calcification in tuberculous lesions of the lymph nodes, the prostate gland, the kidney and other organs is customarily accepted as indicative that the diseased region is walled off and that immunity is well established especially in that region. In a period of nineteen years a diagnosis of renal tuberculosis was made in approximately 1,817 cases at the Mayo Clinic, there was roentgen evidence of definite calcification in the kidney in 131 of these (7.1 per cent). The diagnosis was based on shadows in the roentgenogram coincident with cystoscopic or laboratory evidence of tuberculosis, such as the finding of bacilli, positive results of inoculation of guinea-pigs, the characteristic pyelogram, the usual cystitis, nodules in the genitalia or a functionless occluded ureter. The types of calcification seen in the roentgenogram were multiple scattered small areas, single or localized areas 1 cm or more in diameter and large, irregular, diffuse areas involving either a large portion or the entire kidney. In the first group the small scattered areas are generally caused by deposits of lime. They are occasionally seen singly, and appear as elongated irregular faint streaks or as multiple punctate areas, scattered over a large portion of the kidney usually in one of the poles. Unless the renal area in the roentgenogram is carefully examined, such areas may easily be overlooked. The second group is the type most easily confused with stone. The shadows are usually of several varieties: a shadow of irregular outline, with a consistence dimmer than that seen with renal stone and varying in size from 1 to 4 cm, a shadow characterized by great irregularity in its consistence and outline, somewhat resembling filigree work, and definite shadows with a density and contour suggestive of stone.

21 Crenshaw J. L. Renal Tuberculosis with Calcification. *J. Urol.* 23: 515 (May) 1930.

The size of the shadow does not indicate the extent of the tuberculous lesion. A shadow only 1 or 2 cm in diameter may be present in a tuberculous lesion and involve the entire pole or even the complete kidney. The third group is characterized by large regular round shadows of variable density in their different portions. Shadows caused by complete caseation of the kidney may assume the outline of a complete cast of the kidney and are usually irregularly lobulated. The shadow may vary in density in different portions of the kidney, some are so dim as to be scarcely discernible, whereas others are definitely outlined. Occasionally with complete or extensive calcification, the calcium deposit may be so slight that an accentuated normal renal outline appears in the roentgenogram and it may be difficult to determine whether it is the shadow of an actual lesion. Renal tuberculosis with calcification may be distinguished from renal calculi by certain signs. If the condition under consideration is due to the presence of renal calculi evidence of cortical necrosis is not seen in the pyelogram, the shadow of the stone is included in the calices rather than in the cortex, the vesical changes that are characteristic of tuberculosis are absent, and stained smears and inoculation of guinea-pigs give results that are negative for tuberculosis.

In this group of 131 cases of renal tuberculosis with roentgen evidence of calcification, nephrectomy was performed in 82 and medical treatment was given in 49. There were 99 male and 32 female patients. The average age for the group was 41.39 years. The average age of all the patients with renal tuberculosis with and without calcification was 35.9 years. In 28 cases (22 per cent) urinary frequency or any inflammatory changes in the mucosa of the bladder that would suggest renal tuberculosis were not present. Of 113 cases calcification occurred in the right kidney in 49 and in the left kidney in 55, it was bilateral in 9. In several cases there was calcification in the ureter and in the prostate gland. Adding the cases in which the patients were practically well to those in which the patients improved, the general health was greatly improved in 34 (85 per cent) of 40 patients treated by surgical means and in 7 (58 per cent) of 12 treated medically. The condition of the bladder was greatly improved in 31 (78 per cent) of the 40 patients who received surgical treatment and in 8 (67 per cent) of those who received medical treatment. The mortality is the same in cases with calcification as in cases without calcification. In general mortality and longevity are more favorable when nephrectomy is performed than when medical treatment is given.

The diagnosis is poor in cases of active pulmonary tuberculosis in which treatment is medical. With total calcification and a normal bladder the prognosis is good with either surgical or medical treatment. Nephrectomy should be performed in cases of renal tuberculosis with

calcification as in cases without calcification, except in those in which there is quiescent total calcification coincident with a normal bladder.

Pyelonephritis—Parmenter, Foord and Leutenegger²² reported three cases of this condition. In these three nonsurgical cases treatment by urinary antiseptics of various kinds and by pelvic lavage was carried out, but the patients continued to have persistent symptoms and cloudy urine. The medical treatment for gonococcal infection of the kidney is unsatisfactory whether this treatment is given by mouth or topically, such as by lavage of the renal pelvis.

Mathé²³ stated that the internist and general surgeon often confuse pyelonephritis with influenza and various abdominal lesions. The distinguishing feature in its distinction lies in a careful urinalysis, which should include culture of the urine in order to ascertain the true nature of infection, as the colon bacillus will often overgrow and outshadow staphylococcus, streptococcus and other organisms. Early catheterization and drainage in acute pyelitis are advised in all cases in which acute hydronephrosis is suspected of being due to obstruction caused by congestion, the result of inflammatory processes in the ureter and pelvis which lead to greater narrowing of the physiologically constricted portions of the ureter.

Mathe suggested as a modern treatment for chronic pyelonephritis the systematic eradication of all possible foci of infection, the elimination of stasis in the upper and lower parts of the urinary tract, drainage and lavage as a routine procedure, alternating silver nitrate with the penetrating dyes, and the employment of local immunization by the injection of the filtrate directly into the renal pelvis.

Of the 347 patients observed by Mathé over a period of years, 45 were not improved. Thirty of these presented stasis in either the upper or the lower part of the urinary tract which was an unquestionable factor in lowering the resistance of the kidney, making it more susceptible to infection. One hundred fifteen patients improved slightly, improvement consisting of more or less transitory amelioration of symptoms, the urine, however, continued to show infection. Nephrectomy was performed on 15 patients.

Perinephritic Abscess—Campbell²⁴ presented a clinical study of eighty-three cases of perinephritic abscess. This disease is of extrarenal or intrarenal origin and in most cases is caused by bacterial metastasis.

²² Parmenter, F. J., Foord, A. G., and Leutenegger, C. J. Gonococcal Pyelonephritis, *J. Urol.* **24** 359 (Oct.) 1930.

²³ Mathe, C. P. The Differential Diagnosis and Modern Treatment of Pyelonephritis, *J. Urol.* **24** 119 (Aug.) 1930.

²⁴ Campbell, M. F. Perinephritic Abscess, *Surg. Gynec. Obst.* **51** 674 (Nov.) 1930.

Although the predominant symptoms are fever, pain in the costovertebral angle, leukocytosis and reflex urinary frequency, a lesion other than perineal abscess may be suggested both subjectively and objectively. With this confusion of symptoms and often meager or indefinite clinical data, the diagnosis is difficult. In a third of the cases in the series, the diagnosis is made only at necropsy. Stereoscopic roentgenography is of special value when it shows obliteration of the margin of the psoas muscle on the side of the abscess or lateral spinal curvature away from the abscess. Moreover, when complicating subphrenic abscess is present, elevation and fixation of the diaphragm, with obliteration of the costophrenic sinus, are diagnostic. Technical urologic examination may not be of aid, in two cases in the series it actually confused the diagnosis. The treatment is surgical drainage, although in rare instances a patient recovers without operation. Complications are common and involve the pulmonary and genito-urinary systems in particular. Of the fifty-four patients operated on for perineal abscess, eleven died, an operative mortality of 20.4 per cent. It is noteworthy that most of these fatalities were directly due to complications and the surgical treatment thereof rather than to the primary abscess.

Sisk and Wear²⁵ reported three cases of gonococcal infections of the kidney, ureter and bladder. Johnson and Hill stated that ascending infection to the kidney may occur just as invasion of successive portions of the urethra occurs against the urinary stream. It has been demonstrated that infection in the renal pelvis from the bladder may occur under certain conditions, and in view of the frequency with which the neck of the bladder is involved in gonorrheal infections, this route of infection merits consideration. Simmon favored the hemic or descending route, and the possibility of infection by this route is recognized when one considers the frequency with which gonococcal bacteremia occurs, the low resistance of the patient and the great virulence of the organisms in many cases.

The similarity of gonococcal cystitis to tuberculous cystitis, although mentioned as early as 1902 by Asch and later by Barney and Buerger, has never been sufficiently emphasized. Of the thirty-two cases reported in the literature as gonococcal infections in the kidney and ureter, the diagnosis is doubtful in all but four. The value of fermentation or serologic tests for confirmatory evidence cannot be questioned, but it is believed that the experienced urologic diagnostician, with the aid of an expert laboratory worker, can accurately diagnose this condition by

25 Sisk, I. R. and Wear, J. B. Gonococcal Infections of the Kidney, Ureter and Bladder, *J. Urol.* 23: 639 (June) 1930.

other means. The difficulty in growing the gonococcus on artificial mediums is generally recognized.

Little is known about the treatment of gonococcal infections of the kidneys and bladder. The consensus favors the use of silver salts in the bladder and kidneys.

The prognosis in this type of infection must be guarded. Reaction to treatment begun in the early stages may be satisfactory, but even when the treatment is begun early recovery may be prolonged and tedious to both patient and surgeon.

Resection—Herbst and Polkey²⁶ investigated experimentally, various types of technic in renal resection. They observed the incidence of hemorrhage, fistulas, atrophy and compensatory hypertrophy, and determined the renal function following resections as evidenced by the excretion of phenolsulphonphthalein.

In thirty-seven dogs the kidney was resected under healthy conditions and without disturbing the opposite kidney. Resection of the kidney reduced the weight and phenolsulphonphthalein function in all cases and at all times. Function decreased approximately in proportion to the loss of secreting renal tissue even when small amounts were removed.

Resection of small amounts of renal substance did not affect the life or health of the dog and did not cause compensatory hypertrophy of either the resected or the opposite healthy kidney.

Complete atrophy and complete loss of function of the resected kidney did not occur in thirty-four weeks, although there was always some reduction of weight and size, relative atrophy from disuse was never observed.

[ED. NOTE—The observations of Herbst and Polkey are of value in demonstrating that the function of the individual kidney is impaired permanently in direct proportion to the amount of secreting tissue removed. The fact that compensatory hypertrophy does not commence at once either in the partially resected kidney or in the opposite kidney even when considerable amounts of tissue are removed is of especial significance and somewhat at variance with the usual impression.]

Doubtless, as these authors intimated, there is a definite excess of renal tissue in the body which may be removed up to a certain quantitative amount before the stimulus for compensatory hypertrophy on the part of the remaining renal tissue comes into physiologic activity.]

²⁶ Herbst, R. H., and Polkey, H. J. Renal Resection. An Experimental Study of Postoperative Function, *Surg. Gynec. Obst.* **51**: 213 (Aug.) 1930.

INTERVERTEBRAL DISK EXTENSIONS INTO THE VERTEBRAL BODIES AND THE SPINAL CANAL

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Intervertebral disk extensions into the adjacent vertebral bodies or into the spinal canal have until recently been unknown. Schmorl,¹ in 1926, was the first to direct attention to this pathologic condition. On removal and sagittal sectioning of the vertebral column in routine post-mortem examinations, he found one or more intervertebral disk extensions in the vertebral bodies in 38 per cent of the spines examined. Schmorl named these areas of disk invasions of the bodies cartilage nodes (Knorpel Knotchens). In 1929, both Andrae² and Schmorl³ described similar disk extensions into the spinal canal.

Since Schmorl's first description of the pathologic picture of the intervertebral disk extensions into the vertebral bodies, a number of papers dealing with the clinical phase of this subject have appeared in the German literature. Schanz,⁴ in a paper on the vertebral column and trauma, suggested the possibility of a direct causal relationship between the intervertebral disk extensions or cartilage nodes and symptoms in the back. Dittrich⁵ and Mau⁶ reported single cases of pain in the back and disability, where the lateral roentgenograms showed the

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* The pathologic specimens were removed by the author on autopsy at the Pathologic Institute of the Stadt Krankenhaus Dresden Friedrichstadt, of which Geheimrat Prof. Schmorl is the director. The roentgenograms and clinical cases are from the roentgenologic and orthopaedic departments of the Hospital for Joint Diseases, New York.

1 Schmorl, G. Die pathologische Anatomie der Wirbelsäule, Verhandl. d. deutsch. orthop. Gesellsch. (1926) Kong. 21, p. 3, 1927.

2 Andrae, R. Ueber Knorpelknoten am hinteren Ende der Wirbelbandscheiben im Bereich des Spinalkanals, Beitr. z. path. Anat. u. z. allg. Path. 82: 464 (Sept. 20) 1929.

3 Schmorl, G. Ueber Knorpelknoten an der Hinterfläche der Wirbelbandscheiben, Gesellsch. a. d. Geb. d. Röntgenstrahlen 40: 629, 1929.

4 Schanz, A. Wirbelsäule und Trauma, Arch. f. klin. Chir. 148: 187, 1927.

5 Dittrich. Der roentgenologische Nachweis von Knorpelknoten im Wirbel. Verhandl. d. deutsch. orthop. Gesellsch. (1928) Kong. 23, p. 295, 1929.

6 Mau, C. Der roentgenologische Nachweis der traumatischen Knorpelknotenbildung am Wirbelkörper, Zentralbl. f. Chir. 55: 386 (Feb. 18) 1928.

presence of cartilage nodes Muller,⁷ in five cases, three of which gave a history of pain in the back, found roentgen evidence of intervertebral disk extensions of one or more vertebral bodies

The clinical significance of intervertebral disk extensions is as yet not established Up to the present only seven clinical cases with roentgen evidences of disk extensions into the vertebral bodies have been reported in the literature This condition is relatively unknown, and although a number of papers have been published in German, no paper has yet appeared in English

In this paper I shall describe the pathologic picture and roentgen appearance of the intervertebral disk extensions, and I shall attempt to state their clinical significance

ANATOMY AND PHYSIOLOGY

The intervertebral fibrocartilages or disks are interposed between adjacent vertebral bodies and form the chief bond of union between the vertebrae They consist of an annulus fibrosus, nucleus pulposus and two thin cartilage plates

The annulus fibrosus is a circumferential lamellar layer surrounding the nucleus pulposus It is firm, fibrous and chemically water poor The nucleus pulposus is situated slightly posterior to the center of the disk, commonly at the junction of the middle and posterior third of the vertebral body It is a very elastic and tightly compressed material, which bulges out freely when the confining pressure is removed The nucleus is expansile, soft, water rich, and has the constant tendency to spring out of its confinement in the direction of least resistance The cartilage plates are thin layers of hyaline cartilage, which cover the proximal and distal surfaces of the bodies

The intervertebral disks comprise from one fourth to one fifth of the entire vertebral length They vary in size and shape with the bodies they unite They are widest and thickest in the lumbar region In the cervical and lumbar regions they are thicker in front than behind, giving rise to a forward convexity of the spine In the thoracic region, the disks are flattened and have only a slight effect on the posterior convexity of the dorsal part of the spine

The elasticity of the intervertebral disks rests in the nucleus pulposus In the normal state it is compressed and acts as an elastic cushion or spring Roux⁸ compared the intervertebral disks to a hydraulic press The disks act as shock absorbers and buffers against slight traumas They diminish the jarring effects of the vertebrae in walking, running jumping or other movements of the spine

⁸ Roux, quoted by Schmorl *Verhandl d deutsch path Gesellsch* 22 2-9 1927

⁷ Muller, Walther *Das roentgenologische Bild und die klinische Bedeutung der sogenannten Knorpelknoten der Wirbelsaule, Beitr z klin Chir* 145 161 1928

The disks are in relation in front with the anterior longitudinal ligament, behind, with the posterior longitudinal ligament, proximally and distally, with the adjacent surfaces of the vertebral bodies, and laterally in the thoracic region with the interarticular and radiate ligaments

The intervertebral disks have normally no blood vessels. They receive their nourishment through the cartilaginous plate from the bony marrow by diffusion.

The bodies of the adjacent vertebrae are composed of cancellous tissue covered by a thin coating of compact bone which is normally perforated by numerous small orifices. This thin plate of compact bone acts as a protecting layer of the body against the constant pressure of the disk substance. The interior of the bone is traversed by one or two large irregular canals for the exit of the basivertebral veins from the vertebral body. Over the anterior surface of the bone are several small apertures for the entrance of nutrient vessels.

DEFECTS IN THE VERTEBRAL BODIES

In a sagittal section of a normal spine at autopsy, the expansile fibers of the disks, which rest almost entirely in the nucleus pulposus, are raised above the surrounding surfaces. This highly expansile tissue is separated from the adjacent cancellous stroma of the bodies by a thin cartilage plate and a thin layer of compact bone. In a number of specimens, due to the normal physiologic tension of the disk substance, small semicircular depressions may be noted over the posterior third of the bodies around the location of the nucleus pulposus. These small "doming" defects may be seen in young persons around or shortly after the close of their growing period and represent a slight structural weakness of the vertebral bodies. The cartilage and bony plates are as a rule intact, although in some cases the cartilage plate around the depression is very thin. However, no invasion of the spongiosa usually occurs.

SCHMORL'S CARTILAGE NODES (KNORPEL KNOTCHENS)

In a rather large number of specimens the expansile disk fibers succeed in invading one or more vertebral bodies. The cartilage and bony plates are usually injured, and as a result, the disk substance extends into the body. The extent of the invasion of the spongiosa is small, usually not larger than a pea in area. In one or two cases the break in the continuity of the protecting plates may be so large that part of the disk substance may virtually prolapse or herniate through the opening. It is these intervertebral disk invasions that Schmorl described and named cartilage nodes. In young persons or in a recently invaded body the cartilage node presents a white soft glistening appearance, later it assumes a light blue hue and becomes hard and cartilaginous.

The cartilage node varies in size from that of a pinhead to that of a grape and is most frequently found over the lower thoracic and upper lumbar vertebrae (fig 3A)

ETIOLOGY

The most important etiologic factor is trauma. This may be manifested in the form of mild, repeated injuries to the spine, as for example persons doing hard manual work. This continued trauma may go on for years without causing any signs or symptoms of disability. Yet at autopsy, or in some cases in the lateral roentgenogram, small disk extensions of the bodies are found. In another group of cases a severe sudden injury to the spine, as in a direct blow or fall on the back, may cause a break in the continuity of the protecting plates. With the establishment of an open door, the expansile disk substance invades the body spongiosa. In many of these specimens, small hemorrhages and vascular engorgements are seen around the invaded glistening disk fibers. Infrequently, a direct injury, as a gunshot or stab wound to the vertebral body extending through the bony and cartilage plate occurs, and as a result may lead to the extension of the disk substance into the spongiosa. Schmorl,⁹ in an examination of the spines of 3,000 persons found the latter condition present in only 2, both of whom were war veterans.

Another factor is degenerative or arthritic changes of the cartilage plate. This occurs in a small percentage of persons, particularly in late adult life. The cartilage plate becomes hard and brittle, and under the expansile pressure of an active disk, a tear or break in continuity easily occurs. In some cases, the fibers extend through the small orifices in the bony plate and through pressure atrophy of the intervening trabeculae invade the spongiosa.

In diseased conditions of the vertebral bodies, such as osteoporosis, osteomalacia, tumor metastases or multiple myelomas, the resistance of the vertebral bodies may be considerably lowered. When the intervertebral disks are active, the expansile tension of the disks is often sufficient virtually to compress the bodies, giving them an hourglass or fish vertebrae appearance (fig 8A).

PATHOLOGIC CHANGES OF THE INVADING INTERVERTEBRAL DISK SUBSTANCE

Following the extension of the disk fibers into the vertebral body, a hyperplasia of the cartilage cells of the intervertebral disk takes place and in time, the soft, glistening, expansile invaded disk substance

⁹ Schmorl G. Ueber Knorpelknoten an den Wirbelkorperscheiben, Fortschritt d. Geb. d. Röntgenstrahlen 38 265 (Aug) 1928

becomes hard and cartilaginous. This cartilage node develops principally from the cartilage cell hyperplasia of the intervertebral disk substance. The cartilage cells of the cartilage plates do not seem to take part. In young persons in whom the endochondral growth has not ceased, the cartilage cells from the growing cartilage layer take part. According to Schmorl,¹⁰ the cartilage nodes are to be considered as a "cartilage callous hyperplasia."

In early cases, small hemorrhages, blood pigment and vascular engorgements of the blood vessels are found around the invaded disks.

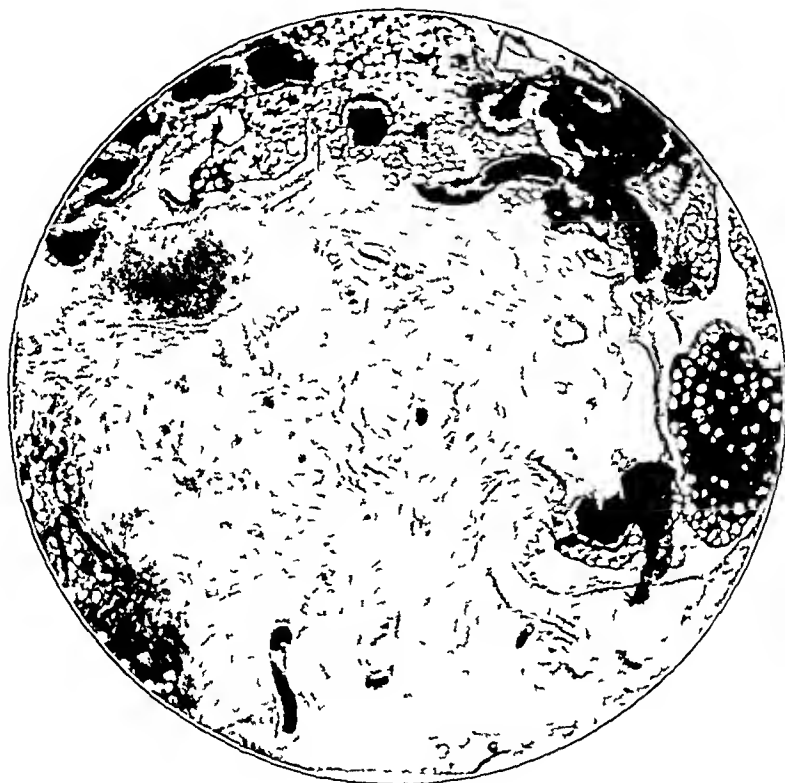


Fig 1—Low power photomicrograph of an intervertebral disk extension into a vertebral body. Note the marked vascular engorgement and dilatation of the vessels surrounding the disk node.

Later vascular infiltration and new vessel formations appear (figs 1 and 2). Around the margin of the cartilage node endochondral ossification and new bone formation set in, which may extend and involve the entire disk node (figs 2 4A and 5A). The extended intervertebral disk node may also undergo cystic degeneration (fig 6A).

10 Schmorl, G. Ueber die in den Wirbelbandscheiben vorkommenden Ausdehnungs- und Zerreissungsvorgänge und die dadurch an ihnen und der Wirbelspongiosa hervorgerufenen Veränderungen. *Verhandl. d. deutsch. path. Gesellsch.* 22:250, 1927.

FREQUENCY OF CARTILAGE NODES

Schmorl, in a review of 2,000 cases at autopsy, found cartilage nodes in 737, or 38 per cent. Of this number, 39 per cent were found in males and 34 per cent in females. For persons from 18 to 59 years of age the figures were: males, 40 per cent, females, 20 per cent, from 60 to 95 years, males, 23 per cent, females, 44 per cent. In early adult life between 18 and 29 years, Schmorl found 39 per cent in males and 18 per cent in females.



Fig 2—Low power photomicrograph of an intervertebral disk node and part of a vertebral body. Note the thick bony barrier at the upper end, and the marked vascular infiltration and engorgement at the left.

INTERVERTEBRAL DISK EXTENSIONS INTO THE SPINAL CANAL

Andrae,² in an examination of 368 vertebral columns at autopsy, found intervertebral disk extensions into the spinal canal in 56 or 152 per cent. These posterior disk extensions are analogous to the cartilage nodes described by Schmorl. They appear as small, firm, pea-sized projections of disk substance on the anterior surface of the spinal canal. Schmorl³ found in a woman of 49, a bony hard, bean-shaped extension of the tenth intervertebral disk, which projected 4 mm into the spinal canal, and which caused a lateral displacement of the cord. Von

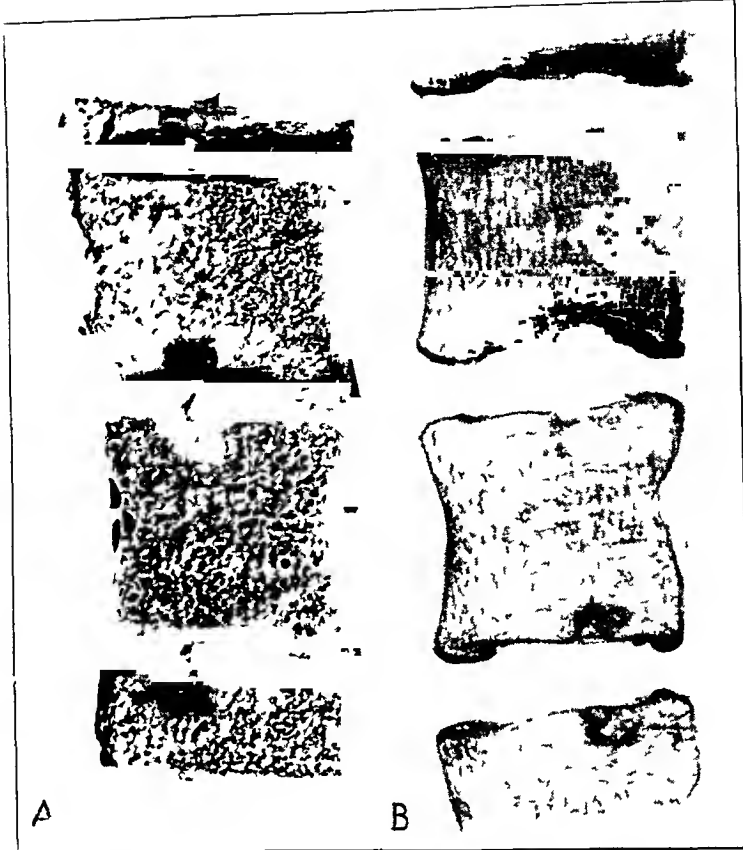


Fig 3—*A* shows a sagittal section of several vertebral bodies with three disk extensions. The upper two nodes have a soft elastic consistency, the lower one is cartilaginous and in places ossified. *B* is a roentgenogram of section *A*. The upper disk node presents a bony defect or area of bone destruction, the lower node presents bone production.

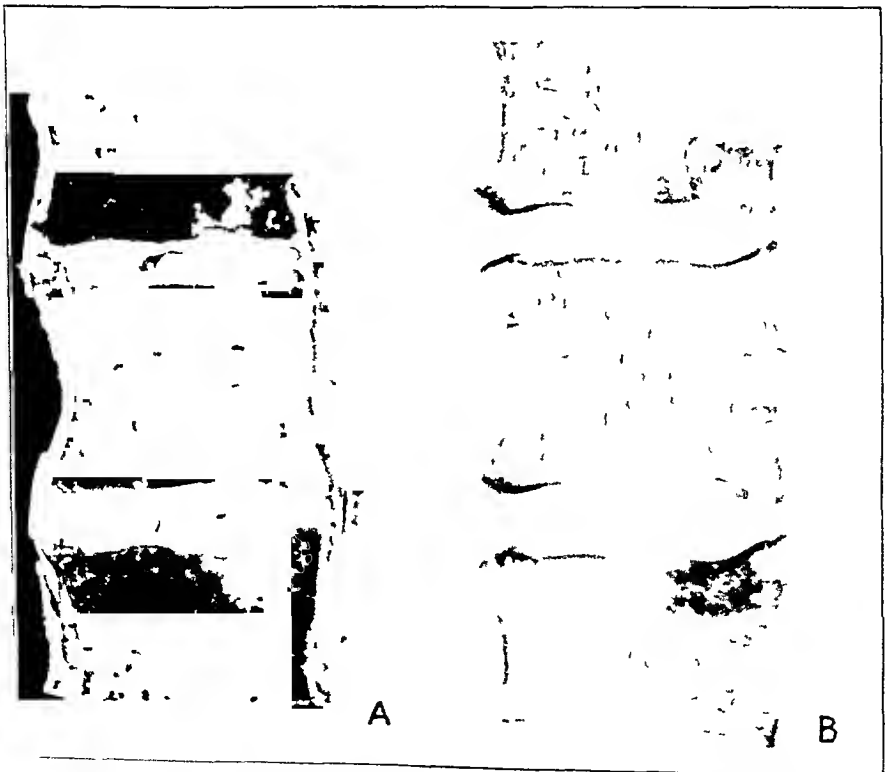


Fig 4—*A* shows two calcified disk nodes. *B* is a roentgenogram of *A*. Note the irregular dense shadow of the lower node.

Pechy¹¹ found in a man of 49, a hard, bean-sized growth of the seventh thoracic intervertebral disk substance in the spinal canal, which produced a backward displacement of the cord. Andrae² and Schmorl³ were of the opinion that this benign growth is an intervertebral disk



Fig 5—*A* shows a sagittal section of the spine with two degenerated disk nodes surrounded by dense compact bone. *B* is a roentgenogram of section *A*. Note the areas of lessened density surrounded by dense sclerotic bone.

node that has undergone secondary changes. In none of the cases reported was a compression of the spinal cord observed.

¹¹ von Pechy, Koloman. Zur Kenntnis der gutartigen Wirbelsäulenzuschnürung im Wirbelkanal, Frankfurt Ztschr f Path 37 562, 1929.

The posterior cartilage nodes are extensions of some of the fibers of the nucleus pulposus into the spinal canal. Normally, the nucleus pulposus is situated at the junction of the middle and posterior third of the vertebral body and is separated from the spinal canal by the posterior fibers of the annulus fibrosus and the posterior longitudinal ligament. As a result of a severe trauma or degenerative changes of

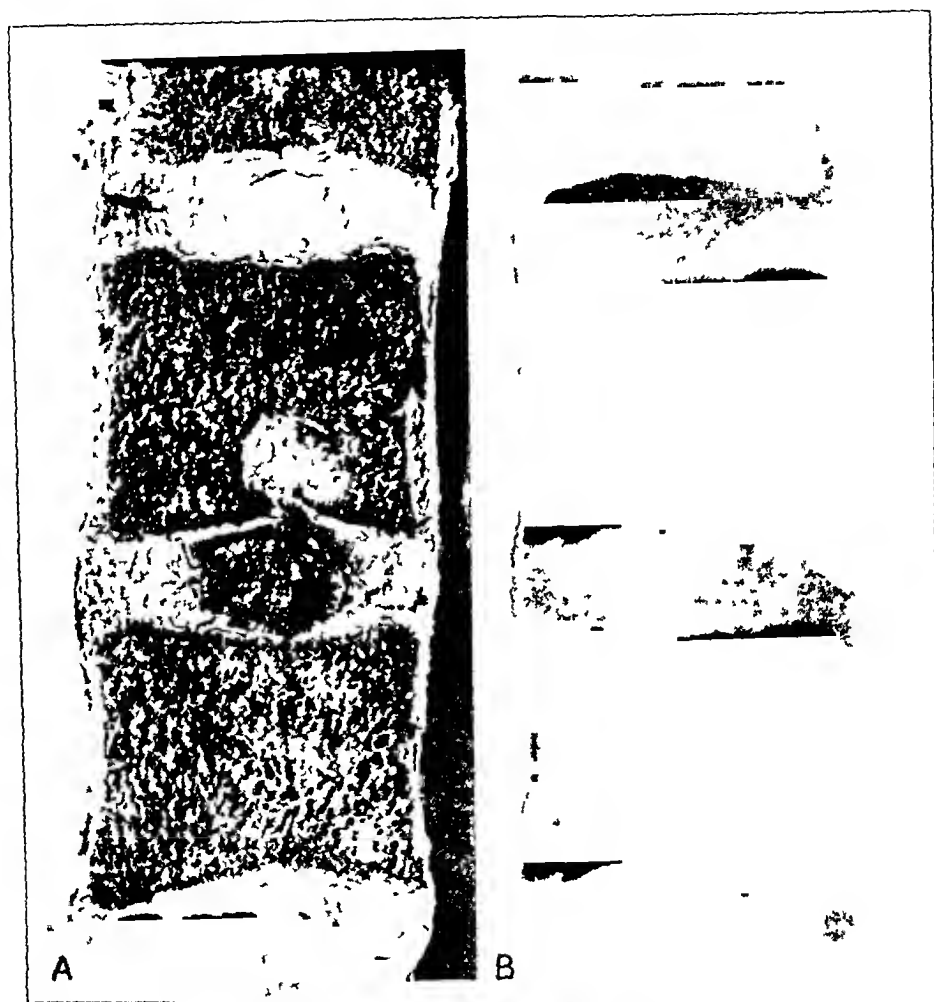


Fig 6—A shows partially degenerated and cystic disk node. B, a roentgenogram of section A, presents a faintly visible small area of osteoporosis.

the annulus fibrosus, an avenue may be established for the extension of the expansile fibers against the posterior longitudinal ligament. The extent of the invasion of the spinal canal is on the whole very slight, yet it is conceivable that the disk extensions may be of such size as either to compress the cord directly or, by becoming loose in the spinal canal, to produce pressure symptoms. Dandy¹² reported two cases in which loose cartilage from the intervertebral disk produced a compression of

12 Dandy, Walter E. Loose Cartilage from the Intervertebral Disk Simulating Tumor of the Spinal Cord. *Arch Surg* 19 660 (Oct) 1929.

the cord which resulted in paralysis of both lower extremities. The patients were men aged 47 and 61 years, respectively. The paralysis followed an injury to the back. A laminectomy was performed and a piece of loose cartilage was found in the spinal canal. Following the operation, the paralysis disappeared.

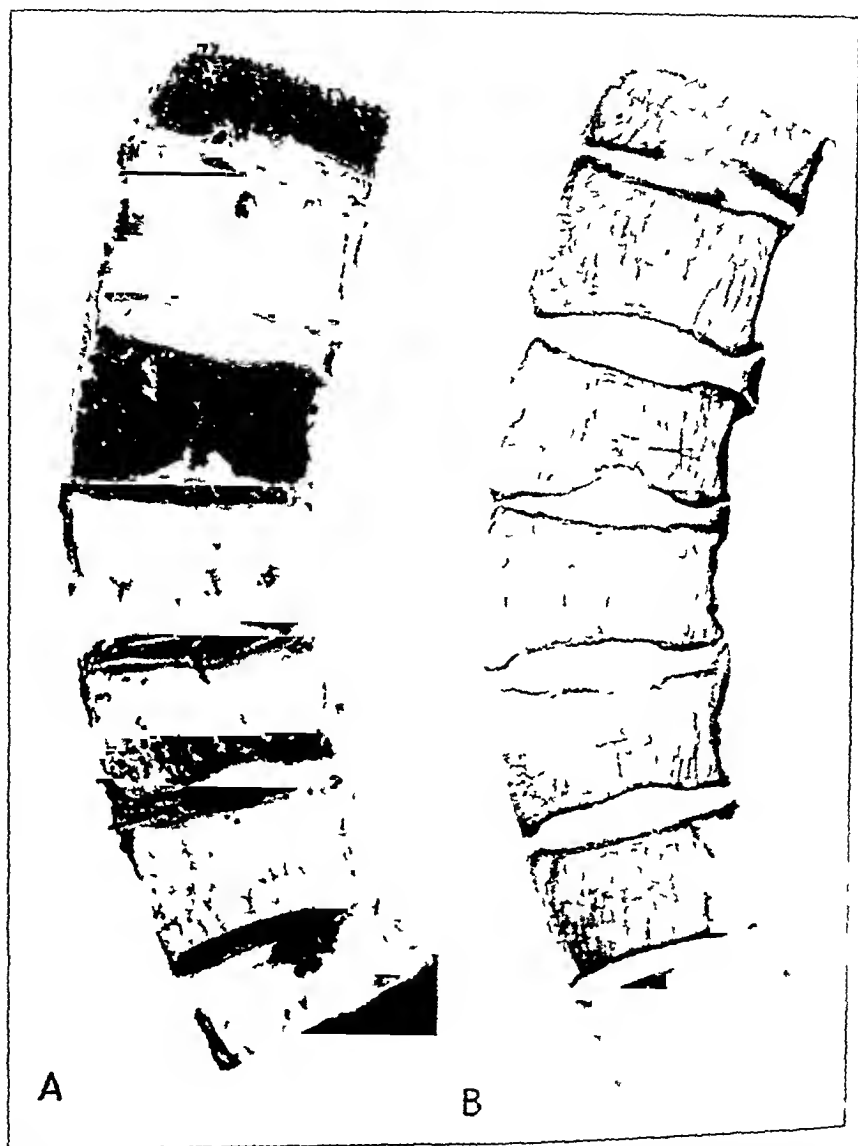


Fig 7—A shows disk extensions in the third and last segment. B, a roentgenogram of section A, shows two defects in the respective bodies.

ROENTGEN STUDIES OF INTERVERTEBRAL DISK NODES

Pathologic specimens consisting of fairly large cartilage nodes in the adjacent vertebral bodies with defects in the cortical plate or surrounded by a dense layer of compact bone are clearly seen on lateral roentgenograms. They appear as small areas of lessened density.

surrounded by a dense shadow. A break in the continuity of the cortical plate is nearly always noted on the film. Posterior cartilage nodes when not calcified or ossified are not visualized. Chasin,¹³ in experiments on the cadaver, demonstrated that structural changes in the vertebral bodies had to be of considerable size to be noted on the roentgenogram. He found that defects of from 1 to 1.5 cm in diameter could not be seen



Fig 8—*A* is a section through the lumbar bodies of a markedly osteoporotic spine. The intervertebral disks are ballooned out. *B* is a roentgenogram of section *A*. Note the extreme osteoporosis and compression or "hourglass" appearance of the bodies.

To determine the extent of roentgen visualization of the cartilage nodes, roentgenograms were made of a number of pathologic specimens with clearly outlined disk nodes. Figure 3*A* is a photograph of a

13 Chasin A. Die Dimensionen der destruktiven Veränderungen in den Wirbelkörpern die roentgenographisch bestimmt werden können, Fortschr a d Geb d Rontgenstrahlen 37 529, 1928

sagittal section of several vertebral bodies, and presents three rather large disk extensions in the bodies. The upper and middle disk nodes are white and glistening and have a soft elastic consistency, while the lower node is cartilaginous and in places ossified. In the roentgenogram (fig 3 B), the upper disk extension presents a semicircular depression



Fig 9 (case 1) —Lateral view showing a depression of the upper surface and a large vacuolated area within the lower half of the third lumbar body.

or area of erosion in the body. The middle disk node can barely be seen. The distal node presents a dense semicircular shadow with evidence of bone production. On the contiguous portion of the adjacent vertebra is a small irregular shadow which is fairly indicative of an ossified node.

Figure 4 *A* presents irregular calcified cartilage nodes. In the roentgenogram, the small irregular upper node is indistinct and can just barely be seen, while the lower node presents a dense irregular semicircular shadow. A comparison of figures 3 *B* and 4 *B* shows that in the former the changes in the bodies are largely destructive, whereas



Fig 10 (case 2) —Note the large defect in the proximal cortical plate of the twelfth dorsal segment

in the latter, the invading cartilage has been converted into a dense calcific structureless node. In section 5 *A*, one notes over the lower bodies two degenerated cartilage nodes surrounded by thick compact bone. In the roentgenogram (fig 5 *B*), they appear as areas of lessened density limited by a dense sclerotic border. Figure 6 *A* presents

a large, isolated and more or less degenerated cartilage node in the vertebral body. In the roentgenogram (fig 6B), this area is only faintly visible as a zone of osteoporosis. In the specimen shown in figure 7A, a disk extension in the third body and a larger disk node in the seventh body is clearly seen. In the roentgenogram (fig 7B), the



Fig 11 (case 3) —Note the semicircular area of lessened density in the lower and posterior half of the eleventh and twelfth dorsal and first lumbar bodies. Note also the patchy appearance of the second lumbar body.

disk extensions are presented as fairly large defects in the third and seventh vertebral bodies of this specimen. Figure 8A is a photograph of a sagittal section of a markedly osteoporotic spine. The intervertebral disks are ballooned out, and the vertebral bodies compressed. Between

the two lower intervertebral disks the body has been compressed and presents an "hourglass" or "fish vertebrae" appearance. In the roentgenogram (fig 8B), the bodies appear atrophic and reduced in size, while the intervertebral disks have ballooned out. One should note also the apparent collapse of the bodies and the extreme osteoporosis.

Clinically, the cartilage nodes are seen in the lateral roentgenogram in only a very small number of cases. Dittrich,⁵ in a review of all the roentgenograms taken at Professor Bayer's clinic in Heidelberg, found cartilage nodes in only one plate. This case was in a man, aged 43, who fell from a considerable height and sustained a compression fracture of the ninth dorsal vertebra. The plates showed small semicircular defects in the cortical layers of the eighth dorsal and in the distal surfaces of the eleventh and twelfth dorsal and the first lumbar vertebrae. Mau,⁶ of the Surgical University Clinic at Kiel, Germany, reported that in a review of all the roentgenograms of the clinic, he found in only one plate the presence of a cartilage node. The plate was of the back of a man, aged 40, who thirteen years before was struck on his back by a falling tree. In the lateral roentgenogram, a cartilage node was seen over the upper margin of the eighth dorsal vertebra. Muller⁷ reported five cases in men varying in age from 21 to 40, in whom one or more cartilage nodes were found in the lateral roentgenogram. At the Hospital for Joint Diseases, in an examination of over 2,000 spines of which roentgenograms had been made for various reasons during the past three years, 9 cases of intervertebral disk extensions were found in 1 or more vertebral bodies.

REPORT OF CASES

CASE 1—M. R., a woman, aged 26, was admitted to the hospital on July 17, 1929, with the complaint of severe pain over the lower part of the back. On April 10, 1929, she fell down a flight of stairs and injured her back. She was carried home and remained in bed for two weeks. She then got up, but still had severe pain over the back, and experienced difficulty in getting about. Examination revealed a slight elevation or knuckle formation over the third lumbar vertebra. Flexion of the lumbar spine was entirely restricted. There was slight tenderness over the third and fourth lumbar spinous processes and over the coccyx.

Roentgen Observations—The third lumbar vertebral body was compressed. There was a definite depression over its upper surface, with a large, more or less irregular, vacuolated area the limits of which were demonstrated as a dense, sclerotic border within the third lumbar body (fig 9). This picture was one of a traumatic extension of the intervertebral disk substance into the vertebral spongiosa.

CASE 2—S. C., a laborer, aged 46, was admitted to the hospital on July 26, 1927, with the complaint of pain over the spine. On April 16, 1926, he fell off a scaffold and injured his back. He was taken into a local hospital in an unconscious state, and remained there for ten days. Since then, he has had severe pain in his back. He is unable to work, carry weights or walk without support.

Motion of the spine was restricted in all directions. There was a slight tenderness over the spinous processes of the eleventh and twelfth dorsal and first lumbar vertebrae.

Roentgen Observations—There was a triangulation of the twelfth dorsal vertebral body with a solution of continuity of the proximal cortical plate. There

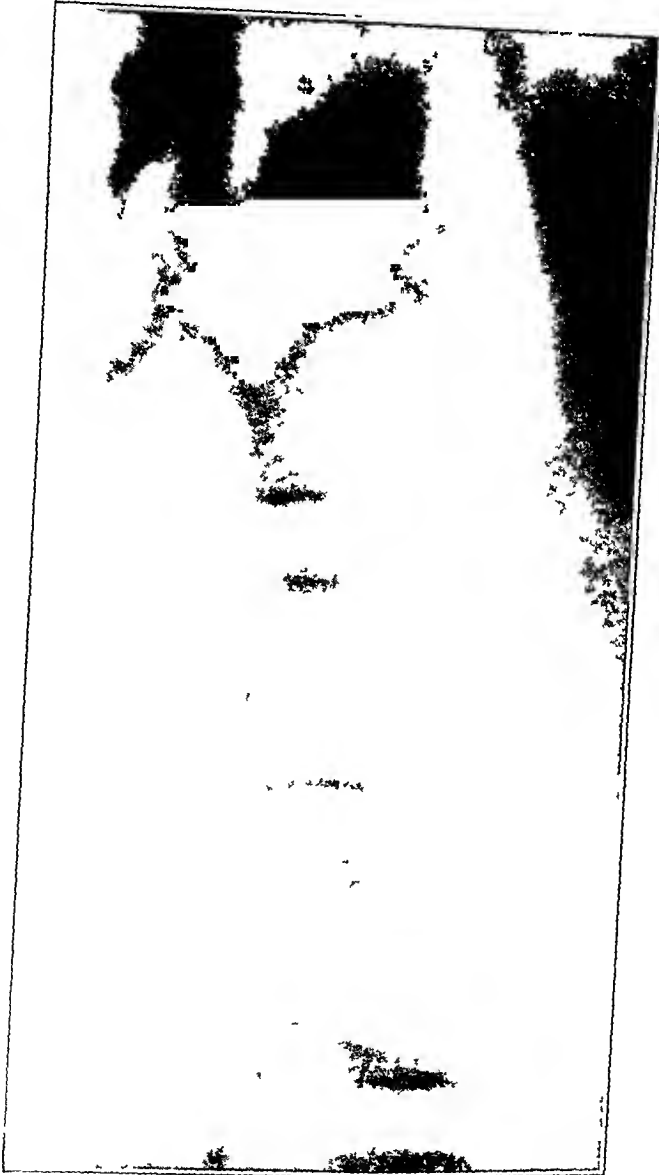


Fig 12 (case 6)—Lateral view showing the semicircular areas of lessened density with sclerosed borders in the upper and lower end of the third lumbar vertebra.

was also a pea-sized area of lessened density in the spongiosa which was surrounded by a dense eburnated border (fig 10).

CASE 3—D S, a cutter, aged 37, was admitted to the hospital with the complaint of pain over the lower part of the back. The patient gave a history of having lifted a heavy roll of cloth, after which he felt a sharp pain in the back.

and was unable to straighten up. He had to be assisted and was taken home. Examination revealed a stiff, rigid spine.

Roentgen Observations—Over the distal articular surfaces of the eleventh and twelfth dorsal and the first lumbar vertebrae were irregular, small areas of lessened density or disk extensions in the spongiosa. These areas were clearly visible and were bordered by a dense surrounding margin (fig 11). The second lumbar vertebrae had an irregular shape with a patchy osteitis.

Comment—In the cases cited a direct causal relationship between trauma and disk extensions in the bodies is evident. In the first two cases, the injury produced a partial collapse or compression of the vertebrae. The disk extensions involved a considerable portion of the bodies and were clearly seen in the lateral roentgenograms. In the third case, a preexisting pathologic condition as a structural weakness of the lower dorsal and lumbar bodies appears to have been present which prior to the injury gave no symptoms. Trauma seems obviously to have had a direct precipitating effect in the production of the spinal picture.

CASE 4—G. J., a school girl, aged 15, was admitted to the hospital with a tentative diagnosis of a tumor of the spinal cord. The patient stated that two weeks prior to her admission, she fell and injured her back. She complained of pain over the left thigh and the knee. The pain was worse at night. Examination revealed no impairment of the motion of the spine and no tenderness. There was a slight atrophy of the left thigh. The attending neurologist felt that the slight atrophy and pain were secondary to a radicular involvement. All laboratory tests were negative.

Roentgen Observations—There were small irregular saw tooth areas on the surfaces of the second lumbar body and a larger semicircular depression over the twelfth dorsal vertebra.

CASE 5—J. M., a shoe operator, aged 37, came to the outpatient department with a complaint of pain over his back. He said that the pain came on after bathing. It was intermittent and was worse in rainy weather. Flexion of the spine was slightly limited.

Roentgen Observations—A small irregular defect or area of bone destruction was seen in the lower cortical plate of the tenth dorsal vertebra.

CASE 6—E. D., a waiter, aged 53, was admitted to the hospital with a complaint of generalized rheumatic pains of over two years' duration. The patient walked slowly and with his body bent forward. Mobility of the spine was restricted in every direction.

Roentgen Observations—Over the proximal and distal surfaces of the third lumbar vertebra were irregular deep depressions in the body (fig 12).

CASE 7—A. B., a salesman, aged 51, was admitted to the hospital with the chief complaint of pain over the right hip and back. Forward bending of the spine was limited and gave rise to pain.

Roentgen Observations—Over the distal surface of the eleventh and proximal surface of the twelfth dorsal vertebrae were several irregular saw tooth areas of lessened density in the vertebral segments.

CASE 8—D O, a woman, aged 31, was admitted to the hospital with the complaint of backache. She had had acute intermittent attacks of pain in the back for the previous two years. Examination of the back revealed slight restrictions of movement and slight rigidity of the lumbar muscles. No local tenderness of the spinous processes was present.



Fig 13 (case 8) —Small irregular depression in the upper posterior margin of the twelfth dorsal body

Roentgen Observations—Over the posterior third of the proximal surface of the twelfth dorsal vertebra was a bean-sized irregular area of lessened density surrounded by a sclerotic border (fig 13).

CASE 9—F H, a woman, aged 70, was admitted to the hospital with the chief complaint of pain over the lower part of the back. The condition came on gradually about two years before. The patient was confined to bed for fourteen weeks. At the time of admission, the pain was severe and shooting. Examination of the back revealed a marked restriction of all movements.

Roentgen Observations—The lumbar vertebrae were markedly osteoporotic. The bodies were compressed and resembled the so-called fish vertebrae (fig 14)

Comment—The etiologic factors involved in cases 4 to 8 are not definite. In case 4, a history of trauma was obtained, but its relationship



Fig 14 (case 9)—Note the marked osteoporosis and moderate compression of the lumbar bodies

to the disk nodes seemed very doubtful. The mode of onset, duration and type of pain in cases 5, 6 and 7, suggest an arthritic involvement of the spine, while in case 8, the well defined, clearly outlined disk extension appears suggestive of a traumatic origin. Case 9 presents atrophic or osteoporotic vertebral bodies in which the intervertebral disks of the lumbar segments were still active, and produced a slight compression of the bodies.

CLINICAL SIGNIFICANCE

The relationship of intervertebral disk extensions into the vertebral bodies to clinical signs and symptoms is as yet not definitely established. Schanz⁴ expressed the view that the disk nodes lower the carrying capacity of the spine and in effect produce an "insufficient" vertebral column, or, as he terms it, an *insufficiencia vertebrae traumatica*. He maintains that the disk extensions are of traumatic origin, and that the clinical picture may be explained by the pathologic observations. On the other hand, Schmorl⁹ said that he feels that the presence of one or more cartilage nodes does not give rise to symptoms. The contention that these nodes diminish the carrying capacity of the spine, he dismissed on the ground that the area involved is usually so small that no appreciable disturbance is likely to occur. Schmorl expressed the belief that the cartilage nodes in young adults lead to the early development of spondylitis deformans. Muller,⁷ in a report of five cases, found symptoms in only those persons showing multiple cartilage nodes in the roentgenogram. He maintained that the disk extensions are not per se responsible for clinical symptoms, but that basically a weakness or "insufficienz" of the vertebral bodies exists.

A preexisting pathologic condition or structural weakness of the vertebral bodies appears to be the underlying basis of a number of disk extensions. The precipitating factor in these cases is usually trauma. The patient who prior to the injury was free from symptoms soon thereafter develops pain and becomes partially or even totally incapacitated. In the lateral roentgenogram, disk extensions may be noted in several bodies, as seen in case 3 (fig 11).

Muller's contention that only multiple disk nodes in the vertebral bodies give rise to symptoms seems inadequate. From my observations, intervertebral disk extensions of traumatic origin, whether single or multiple, give rise to clinical signs and symptoms. In other cases symptoms arise only when a considerable portion of one or more vertebral bodies are invaded. In case 4, although more than one disk node was found, the area involved was small, and as a result no symptoms of the back were present. On the other hand, the clinical picture in case 9 is due to the reduced capacity of the spine, produced largely by the expansion of the disk substance into the atrophic vertebral bodies.

The demonstration of intervertebral disk nodes in the roentgenograms are of vital significance in medicolegal cases. Their recognition and correct interpretation are imperative. The presence of one or more disk nodes in the lateral roentgenogram of a patient who sustained an injury to the back may often explain the clinical picture. In these cases a direct causal relationship between trauma and disk extensions should be assumed to exist, unless roentgenograms taken before the

injury present the same pathologic changes. In all cases of painful and incapacitated spines due to disk extensions, the treatment is firm immobilization in a plaster of paris bandage jacket or by an Albee spine fusion.

SUMMARY

Intervertebral disk extensions or cartilage nodes are pathologic conditions of the spine. They are expansions of the elastic intervertebral disk substance into the adjacent bodies or into the spinal canal.

In the nine cases reported, trauma and degenerative or arthritic changes of the cartilaginous plate were the most important etiologic factors.

Roentgenographically, the disk extensions are seen as small areas of lessened density or small defects in the cortical plate and spongiosa.

Traumatic disk extensions into the adjacent vertebral bodies give rise to clinical signs and symptoms. In other cases symptoms arise only when a considerable area of the bodies is involved.

Intervertebral disk extensions into the spinal cord occur and may produce compression of the spinal cord.

ATROPHY AND FIBROSIS ASSOCIATED WITH LYMPHOID TISSUE IN THE THYROID

STRUMA LYMPHOMATOSA (HASHIMOTO)*

ALLEN GRAHAM, M D

AND

E P McCULLAGH, M D

CLEVELAND

Hashimoto,¹ in 1912, reported four cases of 'a characteristic kind of chronic inflammation' of the thyroid which he designated struma lymphomatosa. He was unable to discover other cases of a similar nature in the literature. We are not aware that any cases corresponding to those described by Hashimoto have been reported as such since the original publication.

Subsequent observers either have failed to recognize or report this particular type of lesion, or have arrived at a different interpretation. The latter assumption seems the more probable, since recent writers have stated that struma lymphomatosa is the early stage of Riedel's struma despite the fact that Hashimoto carefully considered and definitely rejected such a relationship.

Four cases corresponding in every essential detail with those reported by Hashimoto have come under observation at the Cleveland Clinic. These are presented with the hope of stimulating others to record similar cases in order that the condition may be recognized as an entity, or that it may be brought into a proper relationship with other lesions of the thyroid characterized by atrophy of the parenchyma, replacement fibrosis and lymphoid infiltration or with inflammatory processes, bacterial or otherwise.

On account of the longer interval elapsing between the first examination and the operation in our cases we are able to contribute to Hashimoto's original observations the additional fact that the condition tends to progress rather than to retrogress at least for a period of one year.

Our case 4 is the first one, so far as we know, in which the condition was correctly diagnosed clinically.

* Submitted for publication June 5 1930

* From the Department of Surgical Pathology and Surgery of the Cleveland Clinic

1 Hashimoto, H. Zur Kenntnis der lymphomatösen Veränderung der Schilddrüse (Struma lymphomatosa), Arch f klin Chir **97** 219 1912

2 Ewing, James. Neoplastic Diseases ed 3 Philadelphia W B Saunders Company, 1928, p 962

REPORT OF CASES

CASE 1—History—On Dec 14, 1923, a white woman, aged 75, registered at the Clinic complaining of a goiter which she had first noticed eight weeks previously. The goiter had gradually increased in size, the right side more markedly than the left. According to her son, a physician, the swelling was not accompanied by pain, disturbance of pulse rate or nervousness, the only symptoms being vertigo and occipital headaches. The vertigo was dependent on the position in which the arms and head were placed. There was no loss of weight. The patient had always been active and had not had any serious illness. She had borne four children, all of whom were living. Although she had lived for years in a district in which goiter was endemic, she had never had goiter, and there was no history of goiter in any member of the family.

Examination—Examination revealed an elderly, well nourished woman without subjective or objective evidence of hyperthyroidism. There was no evidence of focal infection. All of the teeth had been removed and replaced by an artificial denture. The tonsils were small. The heart and lungs were normal. The right lobe of the thyroid was enlarged and hard, and there was a "rounded nodule"



Fig 1 (case 1)—Anterior, mesial and cut surfaces of the right lobe of the thyroid

in the median line. The temperature was 96.8 F, the pulse rate 60, and the blood pressure 120 systolic and 80 diastolic. The urine contained a trace of albumin, an occasional leukocyte, a few mucous threads and many epithelial cells. The roentgenologist reported that examination of the chest revealed "widening of the upper mediastinum, considerable exudative infiltration over the entire right lung, particularly in the lower lobe, exudative infiltration over the entire left lung, most marked in the apex. The infiltration is not unlike tuberculosis but may be the result of circulatory disturbance." The basal metabolism, blood counts, and Wassermann reaction of the blood were not recorded.

The clinical diagnosis was inoperable carcinoma of the thyroid.

Treatment and Operation—Roentgen therapy was given over the thyroid area on December 15 and 16. The patient was sent home with instructions to return in from six to eight weeks.

On April 24, 1924, the patient reported at the clinic and it was noted that she had reacted well to the roentgen therapy. Her voice had been husky for a few weeks, but she had not experienced dysphagia, dyspnea or loss of weight. According to the history, there was "an irregular, nodular, hard enlargement of the thyroid especially on the right side. The gland was well fixed." The tem-

perature was 99.3 F, the pulse rate 76, and the blood pressure 114 systolic and 68 diastolic. The urine contained an occasional cast and a few leukocytes. The basal metabolism was not recorded. The general physical observations were essentially similar to those noted four months previously. Although the goiter was thought to be malignant, there was no evidence of regional or distant metastases.

On April 25, the right lobe of the thyroid was resected under nitrous oxide-oxygen analgesia and procaine hydrochloride infiltration. After a low collar incision, the muscles were separated in the median line without transverse division. The gland was enlarged bilaterally, and was hard and fixed about the trachea. The right lobe was freed and brought out from its position behind the trachea. It was brittle, and the hemostats broke through without holding. The left lobe was not disturbed. The wound was closed around a flexible rubber drain.

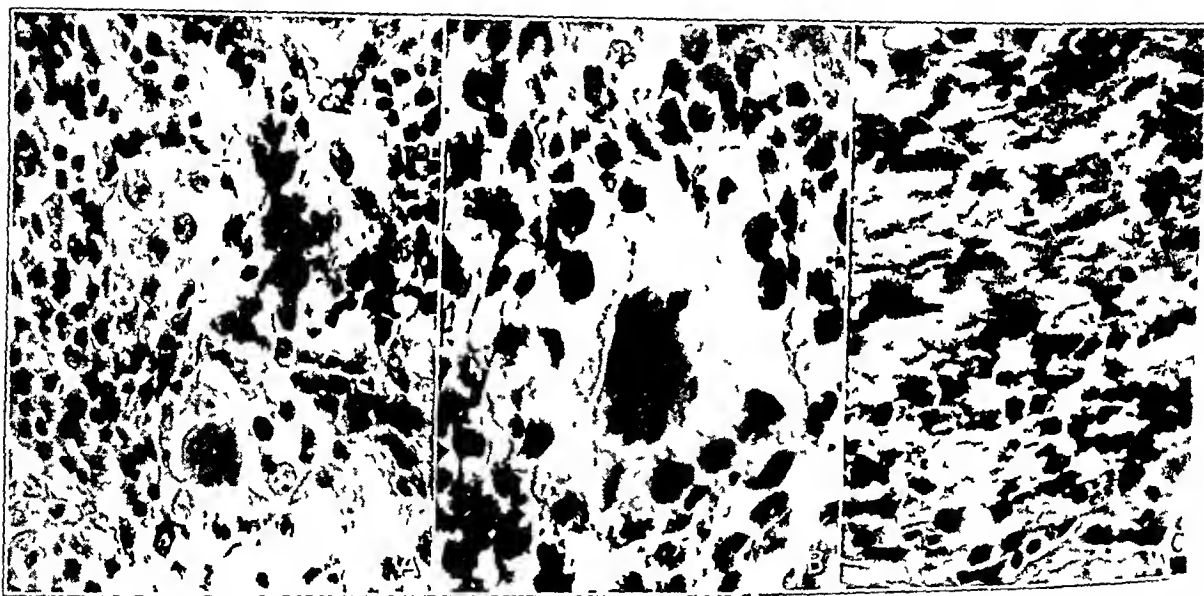


Fig. 2 (case 1)—*A*, atrophic thyroid vesicles and diffuse lymphoid infiltration; *B*, a phagocytic giant cell engulfing the colloid in a degenerating acinus; *C*, dense interlobular connective tissue and disappearance of the epithelium, reduced from a magnification of 600.

Pathologic Report—The tissue consisted of the right lobe of the thyroid (fig. 1). It weighed 90 Gm and measured 8 cm vertically, 5 cm transversely and 6 cm anteroposteriorly. The lobe was considerably enlarged, uniform in structure and consistency and white, and had the contour of a normal lobe. Evidence of infiltration beyond the limits of the intact capsule was not seen. There was increased fibrous tissue resistance on cutting. The cut surface was finely and coarsely lobulated, and very cellular, with a diffuse increase of fibrous stroma. Neither normal thyroid tissue, colloid material, adenomas, nor areas of necrosis were recognizable grossly. Nothing to suggest a neoplasm was observed.

Microscopically, the tissue was divided into small and large irregular lobules separated by dense fibrous trabeculae of variable thickness (fig. 2c). There was marked atrophy of the glandular tissue and replacement fibrosis to the point of complete disappearance of the epithelium in many lobules. In some areas, small

pink-staining thyroid vesicles contained a small amount of colloid material (fig 2 *A*). The nuclei of the epithelial cells varied considerably. Some were small and pyknotic, others were large and hyperchromatic. There was little to indicate active hyperplasia of the epithelium. Mitotic figures were not observed. An

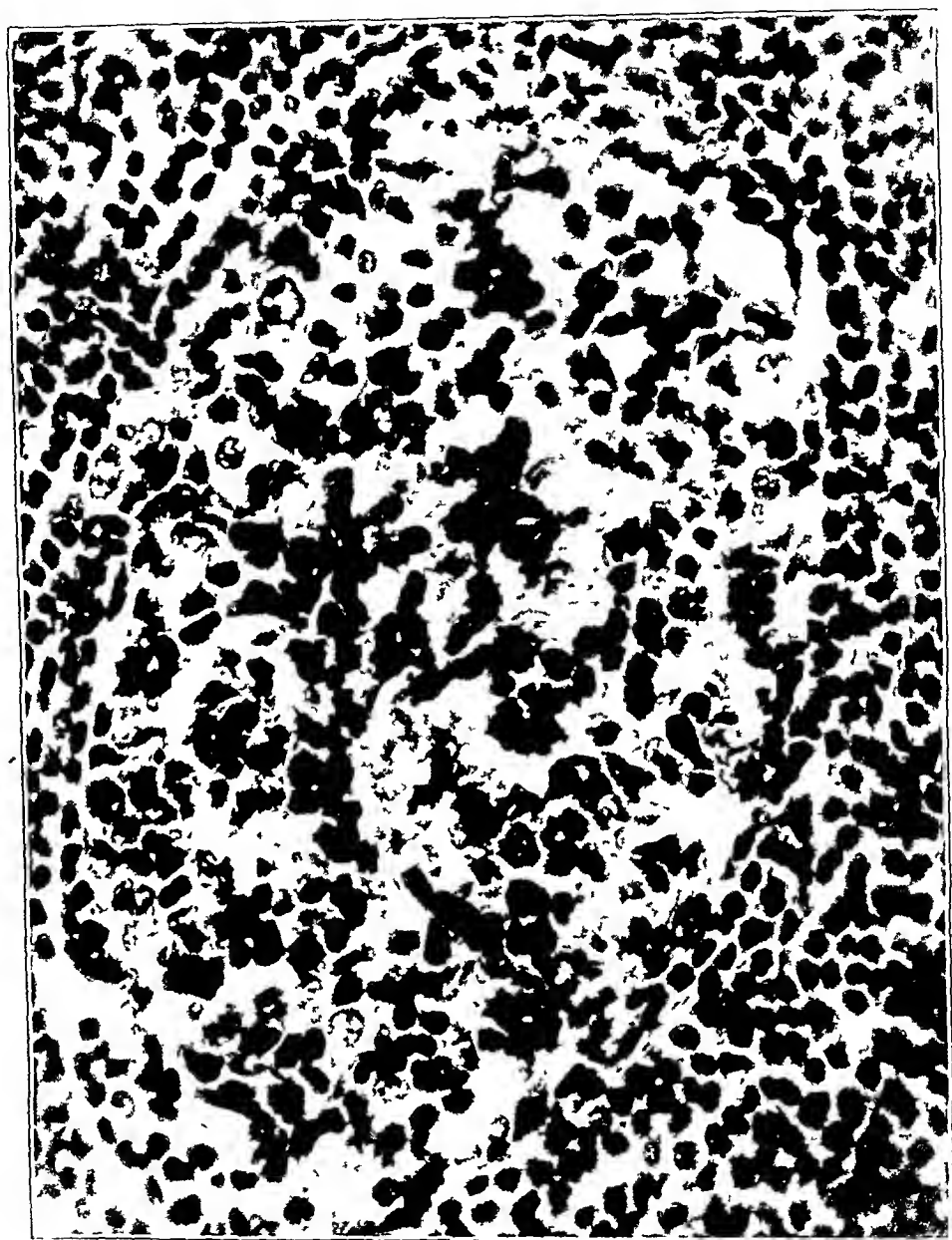


Fig 3 (case 1)—Lymphoid tissue with hyperplastic germinal center, $\times 600$

extensive diffuse lymphocytic infiltration and numerous localized areas of lymphoid tissue with hyperplastic germinal centers (fig 3) were present throughout, there were also a few scattered multinucleated giant cells of the foreign body type. Some of these were present in the acini (fig 2 *B*), apparently phagocytosing the colloid material. There was no evidence of acute inflammation, abscess formation, tuberculosis, syphilis or neoplasm.

The pathologic diagnosis was exhaustion atrophy and fibrosis, with lymphoid infiltration of the thyroid

Postoperative Course—The immediate postoperative convalescence was uncomplicated. The temperature was slightly elevated, but returned to normal on the third day. The drain was removed on the day following operation, and the skin clips on the third day. The patient was discharged from the hospital on May 1, with the wound healed. Following operation she was given thyroxin, which was to be continued under the direction of her physician.

In September, the patient sustained a fracture of the arm as a result of a fall. She recovered satisfactorily.

On Feb. 12, 1926, a letter from the patient stated: "My condition now is very good, excepting my voice. That is husky, as if I had a cold. I think it took nearly a year to recover from my operation. Now I feel as well as I did ten years ago. I lost about 10 pounds but believe I have regained it. I began my business activities in a few weeks after my throat healed, but did not feel in a normal condition for a year."

On Dec. 12, 1929, a letter from the patient's son stated: "She is very well. I do not see any signs of hypothyroidism."

Comment—One of us had an opportunity to examine the patient on the operating table immediately preceding anesthesia. It was noted that the face was swollen, the eyelids puffy and the skin thick and dry, with a definite pallor. The thyroid was enlarged bilaterally, without deformity of the lobes, and there was no evidence of extension to surrounding structures or involvement of cervical nodes. The thyroid did not impress the observer as malignant. After examination of the excised right lobe, it was suggested that the pathologic picture was consistent with clinical myxedema.

Unfortunately, information is not available concerning the amount of thyroxin or desiccated thyroid administered to the patient after her discharge from the hospital. The basal metabolic rate was not determined preoperatively or postoperatively.

CASE 2—History—On Oct. 11, 1923, a white woman, aged 44, registered at the Clinic, with the history that eight months previously facial palsy had developed which she thought might be related in some way to a goiter that had been present for years. At the first observation she was recovering satisfactorily from the palsy. She complained of slight palpitation of the heart and dyspnea on exertion. She was not particularly nervous, had not lost weight and her appetite was good. There was no subjective or objective evidence of hyperthyroidism.

Examination—The results of the general examination were negative, except for obesity, a sty on the left eye, probable dental infection and a "moderate-sized, inactive colloid goiter." The temperature was 98.6 F, the pulse rate 120, and the blood pressure 120 systolic and 70 diastolic. The heart, chest, abdomen and reflexes were normal. The blood counts, Wassermann reaction of the blood and basal metabolic rate were not recorded.

The clinical diagnosis was Bell's palsy (recovering), obesity and adenoma of the thyroid. Operation at a convenient time was advised.

On Oct 20, 1924, the patient returned to the Clinic on account of pressure symptoms attributable to the goiter. The temperature was 98.2 F, the pulse rate 64, and the blood pressure 144 systolic and 66 diastolic. The urine contained a few leukocytes. The patient was admitted to the hospital for operation with a diagnosis of simple goiter.

Operation—On October 22, the lateral lobes and isthmus were resected under nitrous oxide-oxygen analgesia and procaine hydrochloride infiltration. After a low collar incision, the muscles were separated in the median line without transverse division. The thyroid was enlarged bilaterally and symmetrically. There was a slight increase in vascularity. The gland was somewhat paler than normal, suggesting the exhaustion type of hyperplasia. After the resection, the wound was closed around a gauze drain.

Pathologic Report—The tissue consisted of the greater portion of the lateral lobes and isthmus of the thyroid, and weighed 120 Gm (fig 4). The right lobe measured 8 by 4 by 4 cm, the left lobe 6 by 4 by 3 cm and the isthmus 4 by 3.5 by 2 cm. The lobes were considerably enlarged, the right more so than the left. The tissue was white and firm. The capsule was slightly thickened, and



Fig 4 (case 2)—External and cut surfaces of the right and left lobes. Note the fine and coarse lobulation.

the external surface was finely lobulated. On sectioning, increased fibrous tissue resistance was noted. The cut surface was white and finely and coarsely lobulated, with an increase of the fibrous stroma throughout. No normal thyroid tissue, colloid material or adenomatous tissue was recognizable grossly. There was nothing to suggest a neoplasm.

Microscopically, the tissue was divided into irregular areas by fibrous trabeculae of variable thickness traversing the gland from the capsule. The lobular arrangement of the thyroid was imperfectly maintained. In many of the lobules the epithelium was atrophic (fig 5 A), and in a few it was entirely replaced by fibrous tissue (fig 5 B). The remains of the acini were present as small clumps of rarely large, pale-staining, vacuolated cells and larger syncytia-like masses of cytoplasm containing several nuclei. Many of the epithelial masses contained small droplets of colloid and poorly preserved acini. There were extensive diffuse interlobular and intralobular lymphocytic infiltrations (fig 5 C) and numerous large localized collections of lymphoid tissue with hyperplastic germinal centers. Mitotic figures or other evidence of active proliferation of the thyroid epithelium was not observed. Occasional multinucleated giant cells of the foreign body type were present in the areas in which the thyroid epithelium was undergoing atrophy.

There was no evidence of acute inflammation, abscess formation, tuberculosis, syphilis or neoplasm.

The pathologic diagnosis was atrophy and fibrosis of the thyroid, with extreme lymphoid infiltration. The pathologic picture suggested the possibility of clinical myxedema.

Postoperative Course—The immediate postoperative convalescence was uncomplicated. The drain was removed on the day following operation, the skin clips were removed on the third day, and the patient was discharged from the hospital on the seventh day, with the wound discharging slightly.

On November 15, the basal metabolic rate was minus 43 per cent. The patient was given 2 grains (0.13 Gm.) of desiccated thyroid per day.

On Feb. 10, 1925, a letter from her physician stated: "The patient is feeling well, but complains of a swelling of the face and extremities." She was still taking desiccated thyroid for relief from the hypothyroidism.

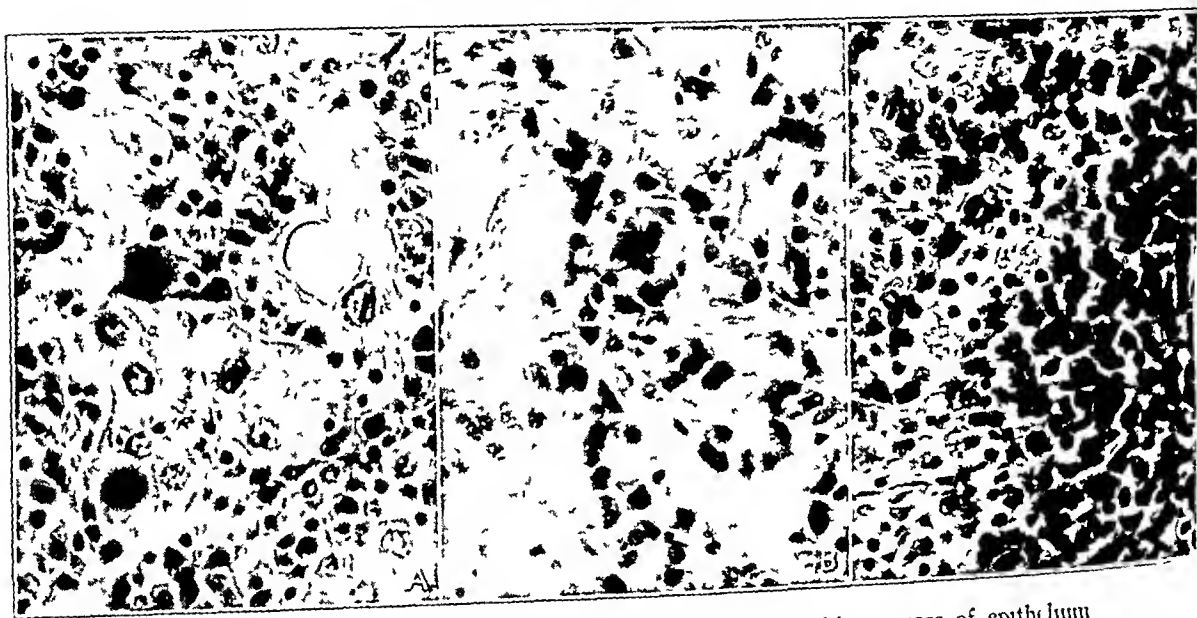


Fig. 5 (case 2)—A, degenerating acini and syncytia-like masses of epithelium; note the vacuoles and droplets of colloid, B, intralobular fibrosis with complete disappearance of the epithelium, C, diffuse lymphoid tissue, reduced from a magnification of 600.

On March 13, 1930, a letter from the patient stated that she had been troubled by hot flashes and sweating for eighteen months. Otherwise she was well when she took one tablet of desiccated thyroid per day.

CASE 3—History—On Feb. 5, 1929, a white woman, aged 53, registered at the clinic complaining of a goiter which had been present for fourteen years. Four years previously the goiter had begun to increase in size, causing dyspnea and a sensation of choking. For one year the pressure symptoms had been increasing in severity, and the patient had been unable to lie on her back. The enlargement of the thyroid was not accompanied by pain, fever, cardiac symptoms, increased nervousness or increased excitability. The appetite had remained unchanged, and there was no loss of weight. The patient was married, had one child living and had had three miscarriages. The menopause had been passed six years previously.

Examination—Physical observations were as follows. The patient was obese, weighing 195 pounds (90.5 Kg). She had many crowned teeth and moderate pyorrhea. The tonsils were enlarged and the pharynx red, but there was no general lymphadenopathy. The skin was of normal texture. The history stated that "the thyroid was greatly enlarged, soft and nodular." The breath sounds over the lungs were wheezy and harsh. There were no râles, friction rubs or areas of increased density. The heart was slightly enlarged to the left. No murmurs were heard. The vocal cords were normal. The temperature was 98.6 F, the pulse rate 80, and the blood pressure 215 systolic and 150 diastolic.

The urine had a specific gravity of 1.036 and contained albumin and numerous leukocytes. The blood sugar amounted to 96 mg and the blood urea to 30 mg per hundred cubic centimeters. The Wassermann reaction of the blood was negative. The red blood cells numbered 4,100,000 and the white blood cells 6,800, the

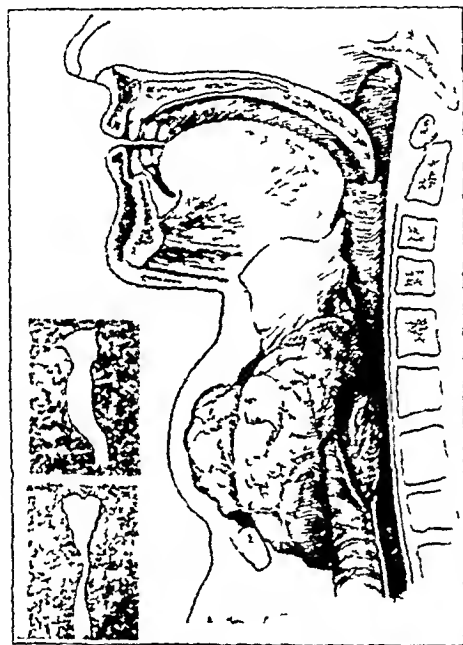


Fig 6 (case 3) —Artist's sketch showing the high position of the upper poles and extension posterior to the trachea, with distortion and compression of the latter.

hemoglobin was 70 per cent, the neutrophils 65 per cent, the small lymphocytes 70 per cent and the large lymphocytes 5 per cent. The basal metabolic rate was not determined.

The clinical diagnosis was adenomatous goiter with tracheal compression, obesity and pyorrhea alveolaris. The patient was admitted to the hospital for operation.

Operation—On February 12, the lateral lobes and isthmus were resected under nitrous oxide-oxygen analgesia and procaine hydrochloride infiltration. After a low collar incision the muscles were separated in the median line without transverse division. The right lobe of the thyroid was from four to five times the normal size and extended behind the trachea. The left lobe was only slightly smaller than the right, and also extended behind the trachea (fig 6). The wound was left open and an iodoform gauze pack was applied.

Pathologic Report—The tissue consisted of the greater portion of the lateral lobes and isthmus of the thyroid, the weight was 175 Gm (fig 7) The left lobe measured 8.5 by 4 by 4 cm, the right lobe, 9 by 3 by 4 cm, the isthmus, 3 cm transversely, 6 cm vertically and 3 cm anteroposteriorly The gland as a whole was greatly enlarged, white and firm The normal contour of the lobes



Fig 7 (case 3) —External and cut surfaces of the right and left lobes. Note the well preserved contour of the lobes.

was maintained. Numerous fine blood vessels were present in the slightly thickened capsule. There was increased fibrous tissue resistance on sectioning. The cut surface was finely and coarsely lobulated. No normal thyroid tissue, colloid material, adenomas, cysts or areas of necrosis were recognized grossly. There was nothing to suggest a neoplasm.

Microscopically, the lobular structure of the thyroid was indefinitely maintained. The lobules were separated by thick trabeculae of dense fibrous tissue. A diffuse fibrosis of many of the lobules (fig 8 c) and well marked atrophy and degenerative changes in the epithelium (fig 8 a) were noted. There was an extensive interlobular and intralobular lymphocytic infiltration, also numerous large localized areas of lymphoid tissue with hyperplastic germinal centers. Many pseudotubercles, apparently resulting from fibrosis and phagocytosis of the degenerating epithelium and colloid material, were present together with a moderate number of eosinophilic leukocytes, but no plasma cells. There were numerous large multinucleated foreign body giant cells, some of which contained droplets of colloid material (fig 8 b) and epithelial debris. Mitotic figures or other indications of active proliferation of the epithelium were not observed. There was no evidence of a neoplasm.

The pathologic diagnosis was exhaustion atrophy and fibrosis with lymphoid infiltration of the thyroid.

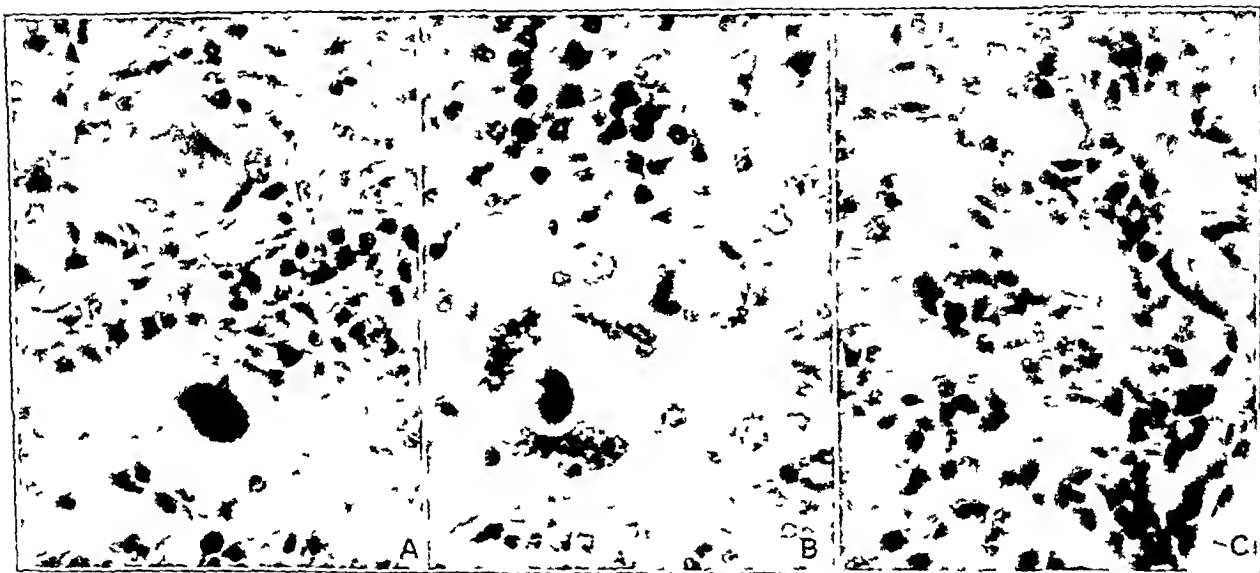


Fig 8 (case 3)—*A*, degenerating epithelium and lymphoid infiltration, *B*, large multinucleated giant cell engulfing the colloid, phagocytosis of the epithelium at the bottom, *C*, young connective tissue replacing the atrophic epithelium, reduced from a magnification of 600.

Postoperative Course—The immediate postoperative convalescence was complicated by infection of the wound, following secondary closure on the day after the operation. The basal metabolic rate was minus 9 per cent on the ninth postoperative day. There was a purulent exudate from the wound at the time of discharge from the hospital on the eleventh postoperative day. The patient has not been heard from since her discharge from the hospital.

CASE 4—History—On July 11, 1929, a white woman, aged 72, was seen in consultation with reference to a goiter that had been considered malignant by other consultants. The following history was obtained:

Six months previously, following an attack of "influenza," she had noticed a painful enlargement of the thyroid associated with tenderness over the gland, with fever. At the onset the goiter had been soft, but gradually it had become hard and had remained so.

Examination—There was moderate uniform bilateral enlargement without evidence of hyperthyroidism or interference with deglutition or respiration. Inspiratory stridor, however, was marked. The gland was hard throughout, closely attached to the trachea and not adherent to surrounding structures. The lobes had a normal contour and there were no nodules, thrill or bruit. Cervical and general lymphadenopathy were absent. The lower extremities were slightly edematous. The only roentgenographic observations in the chest were enlargement of the heart and fibrosis in the hilus of each lung. There was no evidence of metastasis.

The clinical diagnosis was thyroiditis (struma lymphomatosa). Operation was advised.

Second Examination—On November 6, the patient returned to the clinic, having had no treatment since the previous examination. The additional data obtained were as follows. She was born in Ireland, came to the United States at the age of 15, and had lived in Cleveland ever since. She had never had goiter, and there was no history of goiter in her family. The patient was obese, weighing 189 pounds (85.6 Kg.). The temperature was 98.6 F., the pulse rate 84, and the blood pressure 135 systolic and 100 diastolic. Since the previous examination there had been further enlargement of the thyroid, particularly on the right side. The inspiratory stridor was more marked, and the voice had become husky. Laryngoscopic examination revealed evidence of pressure on the larynx anteriorly, obscuring the arytenoid folds. The vocal cords were normal. Roentgenograms of the chest showed enlargement of the heart and marked pneumocardiac fibrosis in the lungs. A blood count showed red blood cells, 3,750,000, white blood cells, 5,200, hemoglobin, 70 per cent, neutrophils, 65 per cent, small lymphocytes, 30 per cent, and large lymphocytes, 5 per cent. The Wassermann and Kahn reactions of the blood were negative. The blood sugar content was 99 mg. and the blood urea, 24 mg. per hundred cubic centimeters. The basal metabolic rate was plus 18 per cent. The kidneys excreted 65 per cent of phenol-sulphonphthalein in two hours. Roentgenograms of the teeth revealed pyorrhea and dental caries.

Operation—The patient consented to operation and was admitted to the hospital, where repetition of the basal metabolic test and blood count revealed the following: basal metabolic rate, plus 21 per cent, red blood cells, 4,140,000, white blood cells, 9,100, hemoglobin, 70 per cent, neutrophils, 67 per cent, small lymphocytes, 30 per cent and large lymphocytes, 3 per cent.

On November 11, the left lobe of the thyroid was resected under nitrous oxide-oxygen analgesia and procaine hydrochloride infiltration. After a low collar incision, the muscles were separated in the median line without transverse division. The left lobe was exposed and found to be hard, and symmetrically enlarged about six times the normal size, with preservation of the normal contour. There were no adhesions between the lobe and the adjacent tissues. During resection of the left lobe it became necessary to divide the pregladular muscles transversely in order to deliver the upper pole. Since operation was undertaken for relief from obstruction and the lesion was found to be nonneoplastic, it was considered unnecessary to resect the enlarged right lobe. The wound was closed around a rubber-tissue drain. A transfusion of 500 cc. of whole blood was given shortly following operation.

Pathologic Report—The tissue removed consisted of the left lobe of the thyroid, the weight was 105 Gm. (fig. 9). It measured 9 cm. vertically, 5 cm. transversely and 6 cm. anteroposteriorly. The lobe was greatly enlarged and the normal contour was maintained. The external surface was coarsely irregular but not nodular. The capsule was thickened, and a small amount of muscle tissue

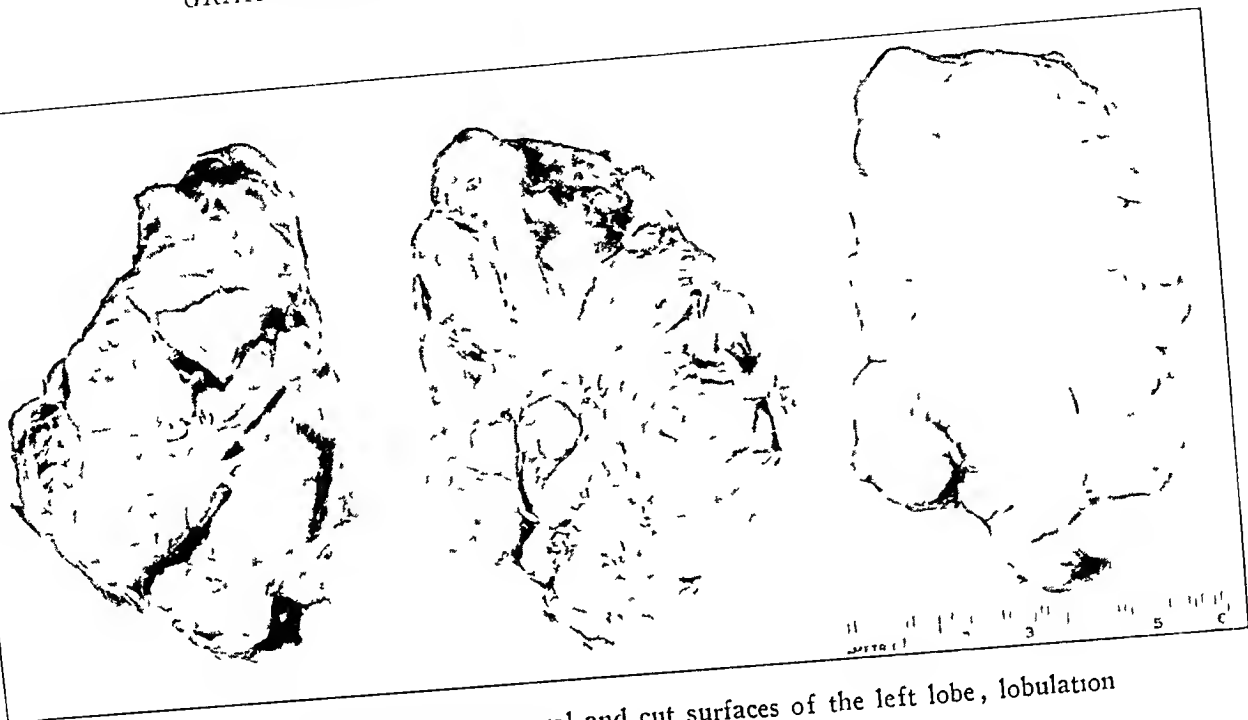


Fig 9 (case 4) —Anterior, mesial and cut surfaces of the left lobe, lobulation obscured by the diffuse fibrosis

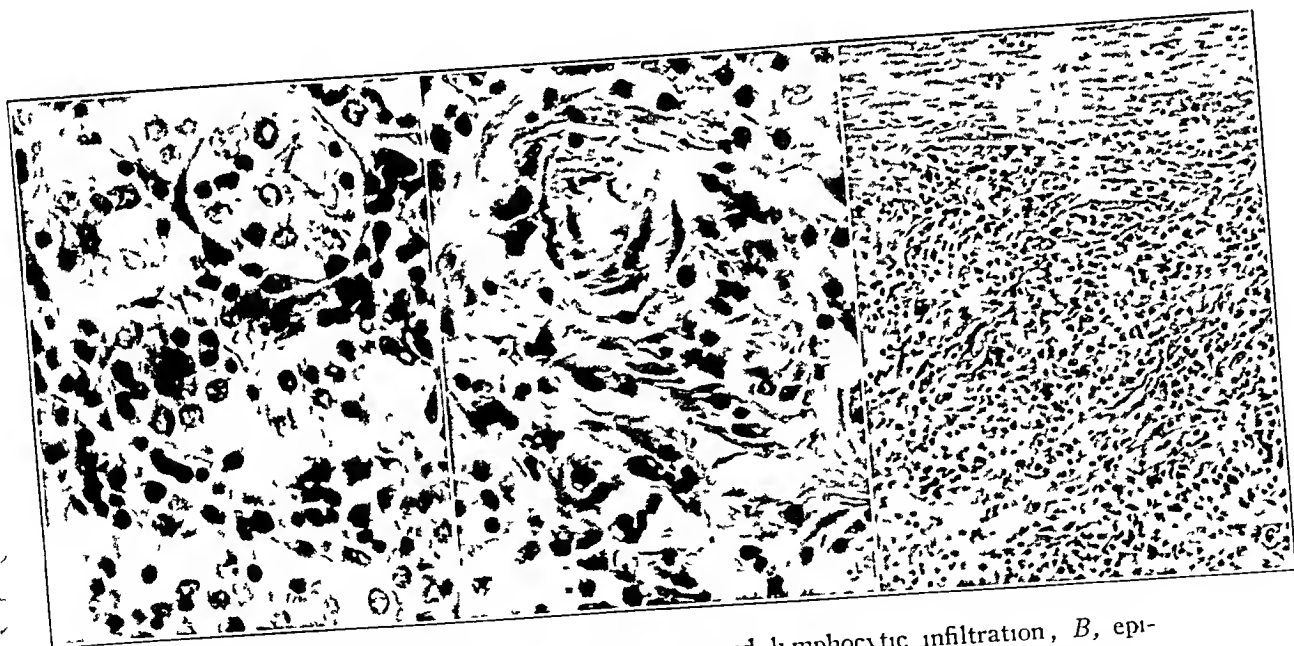


Fig 10 (case 4) —A, degenerating acini and lymphocytic infiltration, B, epithelium being replaced by collagenous fibrous tissue, both A and B reduced from a magnification of 600, C, interlobular and intralobular fibrosis, with complete disappearance of the epithelium, reduced from a magnification of 200

was loosely attached to the anterior surface. The tissue was uniform, firm, rubbery and white throughout. There was a deep groove on the mesial surface for the trachea. The vascularity was not great. On section, the gland cut with increased fibrous tissue resistance. The cut surface was finely and coarsely lobulated and very hard. No normal thyroid tissue, colloid material or adenomas were recognized.

Microscopically, sections from various portions of the lobe showed essentially similar changes. There was a marked diffuse increase of interlobular and intra-lobular fibrous tissue (fig 10 c), with extensive atrophy of the thyroid epithelium. The lobular structure was indefinitely maintained, and in the lobules numerous pale-staining collections of thyroid cells were visible. In some areas these were arranged in small vesicles containing very little colloid (fig 10 a). Throughout the gland there was a diffuse infiltration of lymphocytes (fig 10 a) and a few localized collections of lymphoid cells or leukocytes were present. The tissue as a whole was poorly vascularized, but sclerosis of the blood vessels was not notable (fig 10 b). There was no evidence of acute inflammation, syphilis, tuberculosis or neoplasm.

The pathologic diagnosis was chronic thyroiditis of the Hashimoto type.

Postoperative Course—The immediate postoperative convalescence was uncomplicated. The drain was removed on the first postoperative day and the clips on the third day. There was a slight amount of serum in the wound. The vocal cords were normal following operation. The patient was discharged from the hospital on the sixth day with the wound healed, the temperature normal, the pulse rate from 80 to 90, the blood pressure 110 systolic and 70 diastolic, and the weight 150 pounds (68 Kg).

On December 6, the basal metabolic rate was plus 20 per cent, the pulse rate 90 and the weight 180 pounds (81.6 Kg). The urine contained a trace of albumin and an occasional leukocyte.

On Jan 30, 1930, the basal metabolic rate was plus 11 per cent, the pulse rate 88, the weight 188 pounds (85.2 Kg) and the temperature 97.2 F.

SUMMARY OF EIGHT CASES

The table is a brief compilation of clinical data from the four cases reported by Hashimoto and the four observed by us.

All of the cases occurred in women. At the time of first examination the youngest was 40 years of age, the oldest was 76, and the average age was approximately 55.

None of Hashimoto's patients had lived in a goitrogenous district. All of our patients had lived for years in a district in which goiter is endemic. A history of goiter in the family was not obtained in any case.

In cases 1 to 5 in the table the discovery of the goiter marked the beginning of the complaint, and the duration of the goiter at the first examination varied from three days to seven months with an average of approximately two and a half months. In cases 6, 7 and 8 asymptomatic goiter of eight months' to many years' duration antedated the complaint. In two of these cases 6 and 7, the onset of symptoms was not accompanied by any appreciable change in the goiter. In the third

case 8, following influenza³ the onset of symptoms was associated with an increase in the size of the goiter, pain, tenderness and fever. Possibly the longer duration of the goiter and symptoms in our cases as compared with those of Hashimoto may be related in some way to residence in a goitrogenous district.

Struma Lymphomatosa (Hashimoto) A Compilation of Clinical Data from Eight Cases

Case	Date Examined, Author	Sex, Age	Duration Symptoms	Clinical Diagnosis	Operation	Postoperative Course
1	11/21/07 Hashimoto	F 61	Goiter 7 months no symptoms	Struma parenchymatosa	11/22/07 Bilateral resection	Fatigue and hoarseness following operation, 3/7/11, well
2	5/30/09 Hashimoto	F 40	Goiter 40 days, symptoms 30 days, dysphonia, headache, disturbed appetite	Struma maligna (?)	7/2/09 Bilateral resection	Weakness and inability to work for 9 months 1/27/11, face anemic, moderately nourished, ankylostomiasis
3	6/19/05 Hashimoto	F 55	Goiter and symptoms 1 month, headache and sense of constriction about shoulders	Struma fibrosa	6/20/05 Bilateral resection	Hoarseness, weakness, anorexia, coldness, recurring edema improved by thyroid therapy, 3/20/11, slight hoarseness, no recurrence of goiter
4	9/19/07 Hashimoto	F 45	Goiter 3 days no symptoms	Struma fibrosa	10/20/07 Bilateral resection	Persistent weakness and edema of face recurrence and regression of goiter, 3/10/11, voice husky, thyroid swollen and firm
5	12/14/23 Graham and McCullagh	F 75	Goiter and symptoms 8 weeks, headache, vertigo, hoarseness after roentgen treatment	Carcinoma, inoperable, roentgen treatment, operation 4 months later	4/25/24 Resection right lobe, Wt 90 Gm	Voice husky, hypothyroidism relieved by thyroxin recovery in one year, 12/12/29, well
6	10/11/29 Graham and McCullagh	F 45	Goiter many years symptoms of pressure, palpitation, dyspnea	Adenomatous goiter	10/22/24 Bilateral resection, Wt 120 Gm	Hypothyroidism, basal metabolic rate -43% improved by desiccated thyroid, 3/13/30, symptom free on one tablet daily
7	2/5/29 Graham and McCullagh	F 53	Goiter 14 years, increasing 4 years, dyspnea and choking sensation	Adenomatous goiter, with out hyperthyroidism	2/12/29 Bilateral resection, Wt 175 Gm	Trace lost
8	7/11/29 Graham and McCullagh	F 72	Goiter 14 months symptoms 6 months (following influenza) pain, tenderness, fever, stridor and husky voice	Struma lymphomatosa	11/11/29 Resection left lobe, Wt 105 Gm	Recent case, gradually improving, basal metabolic rate 12/6/29, +20%, 1/30/30, +11%

The symptoms associated with the goiter have been variable, inconstant and, with few exceptions, not pronounced. In two cases, 1 and 4, there were no symptoms other than the goiter. In the remaining six cases the following symptoms were recorded: headache in 3 cases, vertigo in 1, palpitation in 1, disturbance of appetite in 1, pain, tender-

3 This is the only case in the series in which a definite history and physical signs of an acute infection were associated with the onset of the symptoms.

ness and fever in 1, a sense of constriction in the shoulders in 1, hoarseness in 1 (following roentgentherapy), dysphonia in 2, inspiratory stridor in 1, dyspnea in 2 and a choking sensation in 1. The symptoms noted might be ascribed almost entirely to compression (fig 8) by the enlarged, hard thyroid. It is apparent that there were no symptoms sufficiently distinctive to be of diagnostic importance.

Well defined symptoms of hyperthyroidism have been absent in all cases. Painstaking inquiry into the past history in two of our cases failed to reveal any indication of antecedent hyperthyroidism.

Hypothyroidism was not recognized at the first examination or during the interval (up to one year) between examination and operation in any of the cases. In two of our cases (5 and 6) marked hypothyroidism followed operation. In neither of these do we know whether or not the hypothyroidism was present before operation. There are reasons for believing that it was present in case 5, in which roentgen therapy was instituted four months prior to operation. In Hashimoto's case 3, symptoms and signs suggestive of hypothyroidism were noted following operation. These symptoms decreased on administration of a preparation of thyroid gland. In other cases in the series, symptoms suggestive of hypothyroidism were noted, but the records are not complete enough either to establish or to exclude the condition.

All of the cases in our series occurred in women who were overnourished or obese. One of Hashimoto's patients was described as corpulent, two were moderately well nourished, and one was of large stature. There was no indication that weight was particularly increased with the onset of the goiter or the symptoms. Notable loss of weight and emaciation were not observed.

Chronic or focal infections were noted as follows: leukorrhea for twenty years in Hashimoto's case 2, questionable dental infection in our case 2, pyorrhea alveolaris, enlarged tonsils and a red pharynx in our case 3, and pyorrhea and dental caries in our case 4.

Tuberculosis and syphilis were excluded clinically in all of Hashimoto's cases. In one of these the tuberculin and Wassermann reactions were negative eighteen months after operation. There was no clinical evidence of syphilis in any of our cases. The Wassermann reaction was negative in two of these and not recorded in two. In two of our cases roentgenographic examination of the chest suggested the possibility of pulmonary tuberculosis, but in each case an alternative interpretation was equally warranted.

Disturbances of the cardiovascular apparatus, in the sense of overactivity or incompetence, have not been prominently associated with the clinical course of the disease prior to operation. Such phenomena as general weakness, dyspnea on exertion, edema of the lower extremities,

arteriosclerosis and the presence of a trace of albumin, occasional casts and a few leukocytes in the urine were not more frequently encountered or of greater intensity than might be expected in an equal number of patients of similar age. In three of our cases the blood pressure did not exceed normal limits. In one case (our case 3), at the first examination the pressure was recorded as 215 systolic and 150 diastolic and a tentative diagnosis of hypertonus was made. On the patient's admission to the hospital the same day, the pressure was 170 systolic and 106 diastolic. Two days later it was 164 systolic and 100 diastolic. Preceding operation five days later, it was 130 systolic and 70 diastolic. It remained normal after operation.

The accompanying table indicates the clinical diagnoses made and the operations performed in the eight cases. One of Hashimoto's cases was thought to be malignant, and in all of our cases the question of malignancy was raised either preoperatively, at operation or by the pathologist. One of our patients was thought to have an inoperable carcinoma. In our fourth case the goiter had been considered by other consultants to be malignant. The consistency of the goiter more than any other feature suggested the possibility of a malignant neoplasm. At the same time, the absence of definite indications of malignancy such as extension beyond the capsule, involvement of cervical lymph nodes and evidence of distant metastases indicated clearly the necessity of considering in the differential diagnosis some type of chronic thyroiditis or Riedel's struma.

At operation in each of our cases the surgeon was confronted with the problem of determining whether the lesion was a diffuse carcinoma, a lymphosarcoma, a Riedel's struma or a nonspecific type of thyroiditis. In none of these is it usual to find a uniform bilateral enlargement of the thyroid without deformity of the lobes and without adhesions to surrounding structures. These physical features distinguish struma lypomatosa from all of the aforementioned lesions.

Technical difficulties with the operative procedures have not been pronounced, principally because of the lack of adhesions to overlying structures. The glands have been closely attached to the trachea, and in some instances have extended high in the neck and posterior to the trachea (fig 7). For these reasons dislodgement of the lobes is difficult, but may be facilitated by transverse division of the muscles (our case 4). Hemorrhage during operation has not been alarming. Bilateral resection is probably the procedure of choice, although a resection of one lobe relieved the condition in our first case, and was performed in our last case too recently to evaluate the result.

Except for hypothyroidism (vide supra) the occurrence of which we would emphasize particularly postoperative complications and

sequelae have not been serious. Our experience is in accord with Hashimoto's observation that huskiness of voice is persistent and distressing. In none of the cases has paralysis of the vocal cords been noted.

Restoration to health has been slow in all cases. Recovery required about one year in Hashimoto's cases. Our experience is in accord with this observation. We cannot urge too strongly that hypothyroidism be taken into consideration in all cases following operation. It seems probable that the administration of thyroxin or desiccated thyroid should hasten recovery, as it has been distinctly beneficial in two of our cases and in one of Hashimoto's.

Opportunities for observing the natural course of the disease have been limited. Not more than one month elapsed between the first examination and the operation in any of Hashimoto's cases. In none of these were noteworthy changes in the goiter or in the symptoms recorded during this interval. In two of our cases (1 and 4) the operation was performed four months after the examination. In each of these the symptoms increased in severity, and in one the goiter increased in size. In a third case (case 2) the operation was performed one year after the examination, and during this interval the symptoms became more pronounced, although any notable change in the goiter was not recorded. It appears, therefore, that the condition tends to progress rather than to retrogress, at least for a period of one year.

The pathologic observations in the eight cases were singularly in accord. The photographs and photomicrographs represent the process as observed in our cases (figs 1 to 10).

Macroscopically there was uniform bilateral enlargement of the lateral lobes and isthmus of the thyroid. The gland as a whole was usually several times larger than normal (see table for weights) and was closely attached to the trachea. The capsule was intact, and was not adherent to overlying structures. In all parts a relatively normal contour was maintained. The gland was white and firm or hard. On cutting into it, the resistance seemed comparable to that of cirrhotic liver or fibromyoma of the uterus. The external surface was finely and coarsely irregular and without definite nodules. The cut surface was divided into irregular areas of firm white tissue by fibrous trabeculae of variable thickness passing into the gland from the capsule. The structure was uniform throughout the entire organ. In none of our cases were we able to recognize normal thyroid tissue or colloid material grossly. There were no nodules, tumor masses, adenomas, cysts, areas of calcification, abscesses or noteworthy areas of necrosis. The vascularization of the tissue was not great. The blood vessels were not prominent or particularly sclerotic.

Microscopically the four patients examined by the authors had in common well marked atrophy and degenerative changes in the epithelium, marked diminution in the colloid material, replacement fibrosis, extensive diffuse lymphoid infiltration and localized areas of lymphoid tissue with hyperplastic germinal centers, fibrous thickening of the capsule and marked increase of the interlobular and intralobular connective tissue. In none of our cases was there evidence of acute inflammation, abscess formation, tubercles, caseation or gummas. There was nothing to suggest a neoplasm of any kind. These observations, we believe, are in accord with those of Hashimoto. Further details as to the histologic variations in the individual cases are to be found in the case reports.

Macroscopically and microscopically, the process was such as to suggest that the thyroid was affected universally rather than in localized areas.

COMMENT

The nature of the process under discussion is obscure. No single clinical or pathologic feature of the condition is characteristic or pathognomonic. It is only when the record of the individual cases and of the series of cases as a whole is considered that the composite picture becomes sufficiently impressive to suggest that one may be dealing with an entity that hitherto has not received the attention it deserves.

A critical review of the case reports suggests that such clinical phenomena as have been observed are late manifestations of a well advanced pathologic alteration in the thyroid. The anatomic condition of the gland cannot be reconciled otherwise with the short clinical history. Neither the incipient stage nor the natural end-result has been recognized with certainty, and the condition has not been observed at autopsy, so far as we know.

An acceptable explanation of the pathogenesis of the changes in the thyroid is not apparent. It would be simple enough to follow the line of least resistance and agree with one of the prevailing views, namely, that struma lymphomatosa is the early stage of Riedel's struma. A review of the literature and personal experience with both types of lesions have inclined us to the view that they are quite dissimilar.

Riedel's struma more nearly approaches a true inflammation than does the lesion described by Hashimoto. In the majority of cases Riedel's struma occurs in persons under 40 years of age, almost invariably the thyroid becomes adherent to surrounding structures and the cervical tissues are usually extensively involved, even to the point of complete encasement of the carotid sheath and its contents. Practically always it is a deforming lesion and the outlines of the thyroid lobes are lost. It is frequently a unilateral or localized process, it is generally

surgically immovable, it is usually associated with marked pressure symptoms, in many cases there are objective indications of long-standing goiter, notably in the form of adenomatous nodules and adenomas. In all of the foregoing respects Riedel's struma is in striking contrast to struma lymphomatosa. In view of such clearly defined differences it is difficult for us to understand why it should be necessary to consider struma lymphomatosa as the early stage of Riedel's struma. It seems improbable that the early stage of a lesion should occur late in life and the late stage early in life.

From all standpoints, the nature and extent of the changes in the thyroid in struma lymphomatosa are far more suggestive of an end-result the cause of which is to be sought in a constitutional disturbance. Except for the degree and character of the constantly accompanying lymphocytic infiltration and lymphoid tissue, the process impresses us as a sclerosis, possibly comparable to cirrhosis of the liver or to nephrosclerosis. The fibrosis may be looked on as the natural result of atrophy and degeneration of the glandular tissue. The cause or causes of the primary parenchymal changes constitute a problem for future determination. The usual explanations for sclerosing processes are exhaustion from overwork without an adequate period for recovery, interference with nutrition as a result of circulatory or trophic disturbances, and intoxications. All of these have as a primary effect degenerative changes in the cells or tissue, and fibrosis follows.

The lymphocytic infiltration and hyperplastic lymphoid tissue associated with the Hashimoto type of lesion is worthy of particular attention. That it is not specific is indicated by the fact that there appears to be no essential morphologic difference between the lymphoid tissue associated with struma lymphomatosa and that occurring in such diverse states as status lymphaticus, hypothyroidism, endemic goiter and hyperthyroidism. Of these four constitutional disorders, the lymphoid tissue in the thyroid in cases of hyperthyroidism more nearly resembles that observed in struma lymphomatosa.

We are aware that hyperthyroidism has not been recognized in any of the cases reviewed in this paper. Were it permissible to assume an antecedent hyperthyroidism, however, an explanation of the pathogenesis of struma lymphomatosa would not be difficult.

It is recognized that an insidious transition from hyperthyroidism to hypothyroidism and myxedema may occur. With the change, the thyroid undergoes exhaustion, atrophy and fibrosis. This corresponds to the so-called burned-out exophthalmic goiter. There are trustworthy indications that many cases pursue such a course and come under observation with the symptoms of myxedema well marked but with the antecedent hyperthyroidism unrecognized. Year after year we are increasingly impressed with this fact.

In view of the foregoing considerations, it may be premature to exclude hyperthyroidism as a possible precursor of struma lymphomatosa. It is obvious that further experience is necessary before definite conclusions as to the etiology and pathogenesis can be drawn.

Pending the accumulation of further data, it seems not unreasonable to expect that the clinical recognition of struma lymphomatosa (Hashimoto) will increase if the striking peculiarities of the lesion are borne in mind. These may be summarized briefly as follows: (1) uniform bilateral firm or hard enlargement of the thyroid without notable deformity of the lobes and without definite nodules, (2) close attachment to the trachea without adherence to overlying structures, (3) occurrence in women in middle life or later, (4) absence of symptoms other than those that may be ascribed to moderate compression of the trachea, (5) absence of involvement of regional lymph nodes or evidence of distant metastases, (6) absence of impairment of the general health and (7) absence of signs of local inflammation.

CARCINOID TUMORS OF THE SMALL INTESTINE

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There are two anatomic varieties of carcinoma of the small intestine adenocarcinoma and carcinoid tumor. The former is more common than the latter, but both types are rare. The histogenesis of carcinoid tumors is obscure, and their clinical course is not generally understood. Many investigators have considered them benign, yet a number of cases in which metastasis occurred have been reported.

The purpose of this study is to report 11 cases of carcinoid tumors of the small intestine that have not heretofore been reported and to summarize the literature on the subject. Since metastasis was present in 3 cases, the series is divided into a malignant and a benign group.

MALIGNANT LESIONS¹

CASE 1—*History*—A man, aged 67, had been operated on for cholelithiasis three years previous to admission. During the last year he had had persistent diarrhea with frequent, thin, watery stools. A dull, aching epigastric pain and a feeling of fulness had been present for an indefinite period. The appetite had been poor for the two weeks before death.

Necropsy showed strong fibrous adhesions connecting the liver, gallbladder, transverse colon and anterior wall of the abdomen. The appendix was retrocecal and normal. The mesenteric lymph nodes at the root of the mesentery were enlarged and fused into a large, irregular mass. The liver was greatly enlarged, weighing more than 2,500 Gm. The surface was somewhat nodular. Grayish masses, about 8 cm in diameter, projected several millimeters from the surface. These nodules were scattered throughout the liver, but were especially numerous in the right lobe. Many small nodules, from 2 mm to 1 cm in diameter, could be seen just under the capsule of the liver. The nodules had slightly serrated margins, which were sharply defined. The centers of some of them were slightly depressed. On section, large grayish-yellow circumscribed masses were seen, which replaced a large part of the parenchyma of the liver. Some of the larger masses showed cystlike areas from 1 mm to 1 cm in diameter. These were filled with a translucent, gelatinous material.

In the upper part of the ileum was an ulcerated mass about 2 cm in diameter. The margins were raised several millimeters above the surface of the mucosa.

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1 Cases 1, 2 and 4 are from the Department of Pathology, University of Minnesota, cases 3 and 5 to 11 are from the Mayo Clinic

The center was ulcerated to a depth of 3 mm. The serosa opposite the lesion was thickened, glistening white and contracted. At one end of the mass at the root of the mesentery was a large calcareous nodule. The other portion was composed of grayish-yellow, firm tissue similar to that found in the liver.

Microscopic examination showed a compact mass of tissue replacing all the layers of the wall of the intestine. There was a large amount of fibrous tissue throughout the tumor. The inner zone was composed of numerous acini-like spaces and a few solid masses of cells. The acini-like spaces were large and were composed of two or more layers of cells. The lumina were round, oval, fusiform, or completely irregular. Goblet cells, Paneth's cells, acidophil cells or chromaffin cells could not be distinguished. The cells which formed the acini-like spaces and masses were peculiar, atypical, epithelial cells which had a superficial resemblance to the cells of Lieberkuhn's crypts. In shape they were low cuboidal, quadrilateral



Fig 1 (case 1) —Metastatic tumor in the liver from carcinoid tumor of the ileum ($\times 40$)

or polyhedral. The cells varied only slightly in size. The basophilic cytoplasm was usually scanty, homogeneous and clear. The large nucleus was round to slightly oval. The nuclear membrane was prominent and coarse. The nucleus was vesicular and contained a moderate amount of punctiform chromatin. The solid masses of cells were composed of densely packed, small, similar polygonal cells. Mitotic figures were rare. There was considerable infiltration of lymphocytes and plasma cells. The moderately loose reticular stroma was composed of collagenous fibers. The middle zone of the tumor contained only a few small acini-like spaces. The cells were arranged in irregular blocks and masses. In some masses the peripheral cells were of a cuboidal or low cylindric shape but most of them were polygonal. The cells were frequently so crowded that the nuclei were in contact. The stroma consisted of thick bundles of coarse collagenous fibers that enclosed the groups of cells in a netlike meshwork. Only a few small muscle fibers were present. There was no leukocytic infiltration. In the outer zone near the serosa the solid groups of cells were flattened into columns that



Fig 2 (case 1) —Primary lesion of malignant carcinoid tumor of the small intestine, arrangement of cells in columns ($\times 40$)

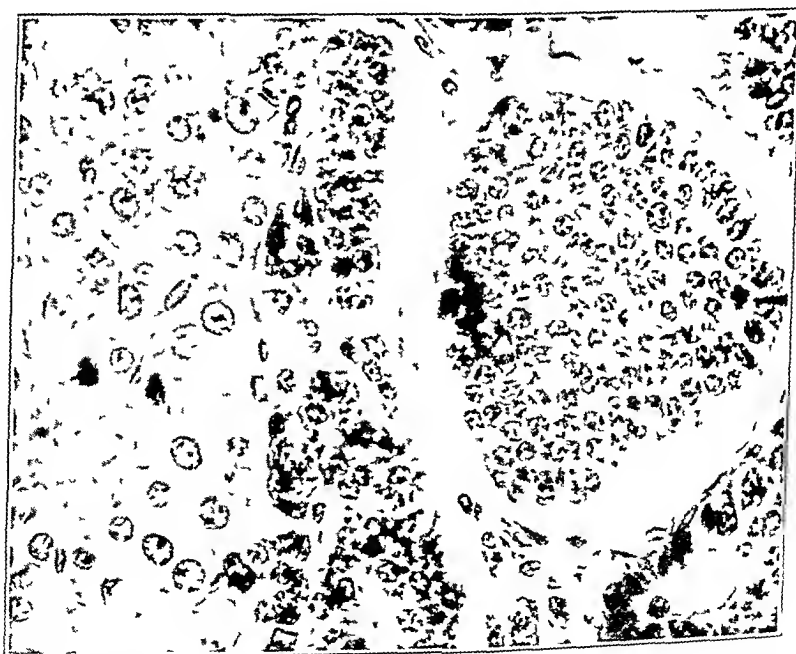


Fig 3 (case 1) —Metastatic tumor in the liver from carcinoid tumor of the ileum ($\times 450$)

is, thin strands or irregular cords of cells. The columns seemed arranged in a somewhat parallel fashion. Toward the serosa, the masses of cells tapered into a blunt point, there were occasional small alveolar masses. The cells were similar in appearance to those in the middle zone.

The metastatic nodules in the liver were rounded, sharply circumscribed masses of cells which compressed the adjacent parenchyma of the liver into atrophic bands. Each nodule consisted of numerous large, irregular sheets of cells. In or near the center of the largest sheets, there was either a capillary or a rounded space filled with a homogeneous smooth acidophilic mucinous substance. In other masses of cells there were irregular areas of central degeneration of variable size and shape. Capillaries were often seen in various parts of the masses. The



Fig 4 (case 2) —A second primary nodule at the site of the anastomosis

individual cells were polygonal and appeared identical to those in the primary lesion. The sparse stroma formed a loose incomplete network about the masses of cells, but did not encapsulate them. A few vessels ran in the connective tissue between the masses (figs 1, 2 and 3).

CASE 2—History—A woman, aged 65, was admitted to the hospital complaining of lack of appetite, belching of gas, nausea, vomiting, epigastric pain, flatulence, constipation and general weakness. Eight weeks before admission, the patient had been awakened during the night by intense pain in the middle of the epigastric region. The pain was sharp, intermittent and cramplike. The patient was nauseated but did not vomit. Some relief was obtained by drawing up the knees on the abdomen. The attack disappeared in four hours. Three weeks after the first attack she had a second attack of severe pain, but at this time she vomited a yellowish fluid. After a short time the severe pain changed into a constant dull



Fig 5 (case 2) —Metastatic nodules in the liver



Fig 6 (case 2) —Primary lesion of malignant carcinoid tumor of the ileum
($\times 40$)

epigastric ache. The appetite became poor. She had lost 50 pounds (22.7 Kg) in weight during the last six months. There was a moderate amount of belching.

The patient appeared to be undernourished and anemic. The abdomen was distended and tympanitic. The edge of the liver was felt just below the costal margin. The results of examination of the urine were negative.

Exploratory operation disclosed a mass in the distal part of the ileum which produced obstruction. Other masses were found in the mesentery and on the surface of the liver. These masses were believed to be metastatic from the primary tumor in the ileum. The tumor in the ileum was removed by resection, and a side-to-side anastomosis was performed between the proximal and distal segments. In the ileum a hard, fibrous, yellowish-gray nodule 16 mm in diameter projected into the lumen for a distance of 14 mm, producing almost complete obstruction. The nodule, on section, was found to be composed of a submucosal hard mass

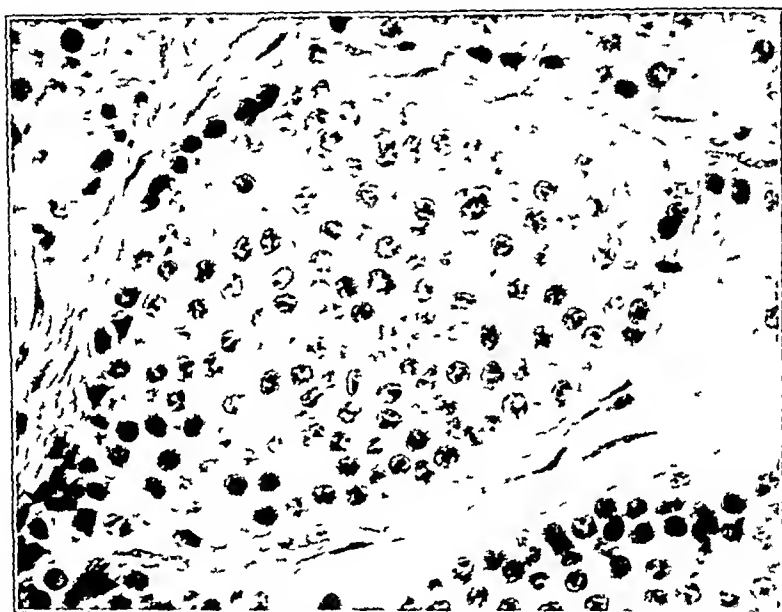


Fig 7 (case 2)—Malignant carcinoid tumor of the ileum ($\times 450$)

with invagination of the wall of the ileum. The serosal surface was rough, thickened and infiltrated. Five days after the operation the wound became suppurative. The patient died fourteen days after the operation.

At necropsy a second hard, fibrous, submucosal nodule 8 mm in diameter was found about 12 cm from the site of the tumor which produced obstruction. The gross appearance of the two tumors was similar. The regional lymph nodes were enlarged. On section they were found to be composed of hard, yellowish tissue. In the mesentery, about 7 cm from its attachment to the ileum, there was a hard, nodular yellow tumor which measured 4 cm in diameter. Underneath the capsule of the liver were numerous small yellowish-white nodules which measured from 2 to 6 mm in diameter. The mass which was felt on the liver at the exploratory operation and believed to be metastatic was found to be a simple cyst 6 cm in diameter. The substance of the liver was filled with numerous small nodules from 1 to 10 mm in diameter. In the middle of the right lobe was a sharply circumscribed hard, yellow tumor 4.5 cm in diameter.

The microscopic examination of sections from the primary and metastatic nodules showed the structure to be composed of the atypical epithelial cells of carcinoid tumors

A diagnosis was made of carcinoid tumor of the ileum with metastasis to the regional lymph nodes, the mesentery, and the liver (figs 4 to 7)

CASE 3—History—A man, aged 60, complained of hourly attacks of pain in the epigastrium. The pain radiated to the lower left quadrant of the abdomen and was followed by moderate residual discomfort. On general examination, nodular masses were found in the right and left upper quadrants of the abdomen. The systolic blood pressure was 94, and the diastolic 70, measured in millimeters of mercury. The hemoglobin was 78 per cent and the leukocytes numbered 5,800. The results of roentgen-ray examination were negative. While the patient was under observation, severe abdominal pain and general tenderness developed

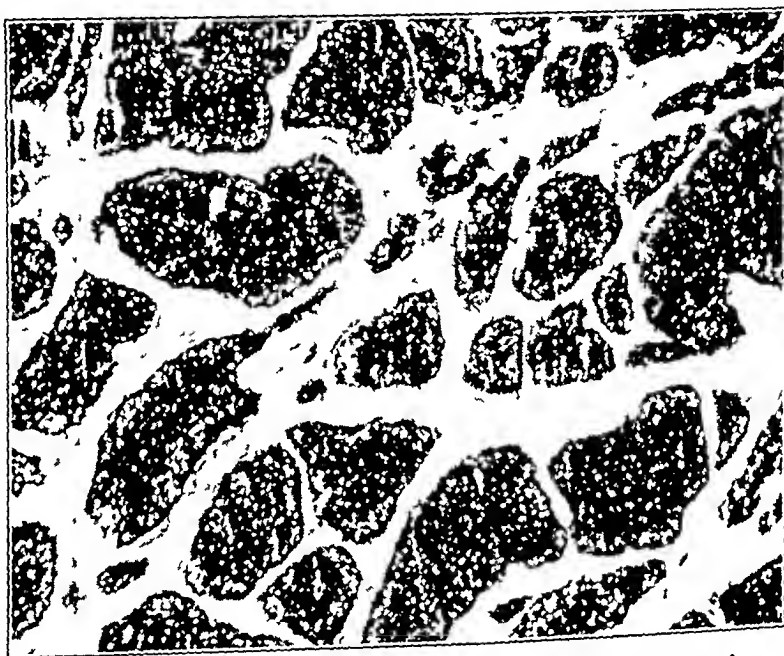


Fig 8 (case 3) —The argentaaffine reaction in the primary lesion of a malignant carcinoid tumor of the ileum ($\times 160$)

suddenly. On exploratory laparotomy, yellow fluid was found free in the abdominal cavity. The perforation was not localized. The patient died the day after the operation.

At necropsy, multiple, firm, elevated, submucosal nodules, from 0.5 to 1.5 cm in diameter, were found in the ileum and jejunum. At two points the nodules appeared large enough and close enough to produce obstruction of the lumen. The ileum for a distance of 20 cm was dilated, the wall was thickened and grayish black, and at some areas there was almost complete necrosis. The mesenteric nodules draining this region were all enlarged. At the attachment of the mesentery there was a single, hard, encapsulated mass 4.5 cm in diameter. The cut surface of this mass was composed of compact yellowish tissue. The liver extended 7 cm below the costal margin in the midclavicular line and weighed 3,200 Gm. On the surface were numerous yellowish, firm nodules which measured from 1 mm to 3 cm in diameter. On section, the liver showed many nodules from

0.5 to 6.5 cm in diameter, scattered throughout the organ in an irregular fashion. The center of many of the larger nodules appeared somewhat soft.

Microscopic examination of the tumors in the wall of the ileum, in the mesentery and in the liver showed them to be composed of undifferentiated polygonal or round, somewhat basophilic, epithelial cells, arranged in columns, cords or irregular masses. The stroma of the tumors in the ileum was composed of bundles of smooth muscle fibers and coarse collagenous connective tissue fibers. The metastatic nodules were all definitely encapsulated. The stroma was small in amount and consisted of a few bundles of collagenous connective tissue fibers (figs 8 and 9).

BENIGN LESIONS

CASE 4—*History*—A woman, aged 52, had had an attack of severe, griping, diffuse abdominal pain on Feb 3, 1929. She was not nauseated and did not vomit.

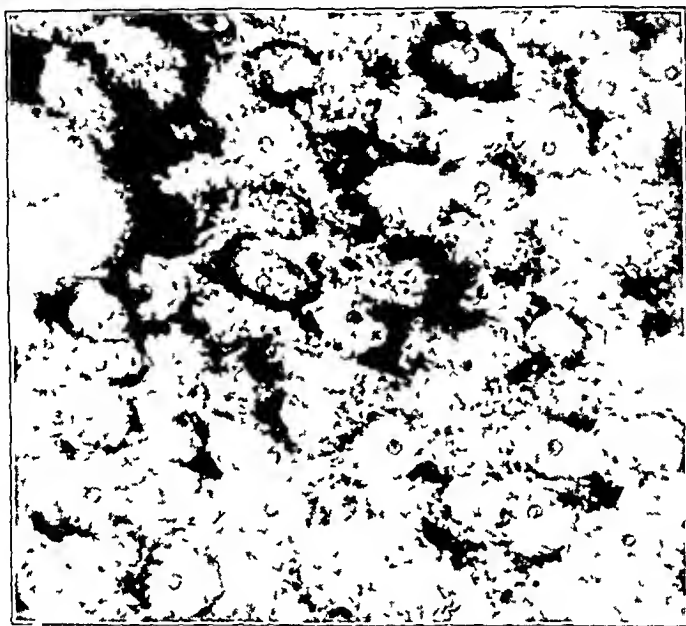


Fig 9 (case 3)—The argentaffine granules in the cytoplasm of a malignant carcinoid tumor of the ileum ($\times 1,200$)

She weighed 200 pounds (90.7 Kg). The abdominal wall was rigid. There was slight general abdominal tenderness. The systolic blood pressure was 125 and the diastolic 90. Complete relief followed the administration of several enemas and one hypodermic injection of morphine.

The patient was not seen again until June 29. She then had a sudden attack of severe cramplike, excruciating pain across the abdomen. The pain was slightly more marked about the umbilicus and was intermittent. Every three to four minutes it reached maximal intensity which lasted for one minute. A hypodermic injection of morphine gave relief for four hours. The pain then recurred and was associated with moderate vomiting. The vomitus was stained with bile. The hypodermic injection of morphine was repeated. The leukocytes numbered 12,000. The abdominal pain became so intense that a third injection of morphine was required four hours after the second dose. This gave relief for about twelve

hours. The bowels had not moved since the onset of the attack. A second examination of the blood showed erythrocytes 4,300,000, leukocytes 12,400 and a negative differential count. The urine was normal.

On June 30, laparotomy was performed. There was considerable free serous fluid in the peritoneal cavity. The serosa of the small intestines appeared somewhat injected. In the ileum about 60 cm from the ileocecal valve, there was a circular scarlike contraction with a central lumen about 8 mm in diameter. The ileum above this marked obstruction was definitely dilated, below it was empty and collapsed. Enlarged mesenteric lymph nodes were neither visible nor palpable. The appendix and all other organs inspected appeared normal. Jejunostomy was done. The obstruction, with a small piece of adjacent intestine, was removed. The patient died about twenty-four hours after the operation, apparently from pneumonia. Necropsy was refused.

The primary tumor consisted of a firm, fibrous mass in the submucosa which encircled the lumen of the ileum. The mucosa over the upper third of the growth was ulcerated. The mass was composed of sheets, columns and masses of polyhedral cells similar to those described in case 3. In a few sections there were a number of rounded masses or clumps with a central irregular space which suggested an acinar arrangement. The largest solid masses of cells were found near the serosal surface of the tumor. There was no infiltration of leukocytes. The abundant stroma was formed by compact, interlacing, coarse bundles of collagenous fibers.

CASE 5—History—A man, aged 72, had had several attacks of severe pain in the lower part of the abdomen during the last year before admission to the hospital. The pain occurred after meals and was relieved by medication. There had been marked constipation during the last year, and three weeks before examination, blood had been observed in the stools. The patient had lost 19 pounds (8.6 Kg) in weight during the three weeks previous to admission.

A filling defect was found in the sigmoid. A clinical diagnosis of carcinoma of the sigmoid was made and a two-stage operation, for the removal of the involved portion of the colon, was performed. The patient died after the resection of an extensive carcinoma of the rectosigmoid, with involvement of the regional lymph nodes.

At necropsy, there was observed in the median portion of the ileum, a firm circumscribed nodule 3 mm in diameter. On microscopic examination this mass was found to be composed of atypical, polygonal or round epithelial cells, arranged in cords, columns and irregular masses. There were a few acini-like accumulations of cells. The stroma was composed of coarse collagenous fibers.

CASE 6—History—A man, aged 61, had complained of dyspnea on exertion for ten years. During the last few months he had been troubled by a persistent cough. A tubercous, ulcerating mass was found on the glottis, which was diagnosed clinically as epithelioma. Two-stage laryngectomy was performed. Death from pneumonia resulted following the second stage of the operation.

A small, firm nodule 5 mm in diameter was found at necropsy in the submucosa of the ileum, 29 cm from the ileocecal valve. Microscopic examination of this nodule showed it to be a submucosal mass of atypical, basophilic polygonal, epithelial cells arranged in columns and irregular masses.

CASE 7—History—A man, aged 59, had had severe trigeminal neuralgia during the fifteen years previous to admission. The results of an examination were essentially negative. Death followed operation for evulsion of the sensory root of the trigeminal nerve.

At necropsy, a firm submucosal nodule, 1 cm in diameter, was found in the ileum about 26 cm from the ileocecal valve. On microscopic examination, the tumor was found to be composed of a number of irregular masses and sheets of atypical, basophilic, polygonal or rounded epithelial cells. Many of the cells were single or in small groups. There was no evidence of a tendency of the cells to arrange themselves in acini or acini-like formations.

CASE 8—*History*—A man, aged 69, had noticed gradually increasing urinary obstruction with nocturia during the six months previous to admission to the hospital. Complete retention had occurred three months previous to examination. Hypertrophy of the prostate gland was found. The patient died three days after suprapubic prostatectomy.

A hard nodule of the submucosa 3 mm in diameter was found in the jejunum, at necropsy. The nodule was composed of atypical basophilic, epithelial cells characteristic of carcinoid tumor, arranged in columns and irregular masses.

CASE 9—*History*—A man, aged 58, had noticed gradually increasing intracranial pressure, beginning five months before. While he was under observation, complete right hemiplegia and aphasia developed. A clinical diagnosis of tumor of the brain was made, and a left decompression was performed. The patient died one day after the operation.

A submucosal nodule 5 mm in diameter was found in the jejunum at necropsy. On histologic examination, the tumor was found to be composed of the characteristic carcinoid tumor cells. In some areas of the tumor there were a few small acini-like spaces, but the cells which lined these spaces did not appear identical to the atypical carcinoid tumor cells.

CASE 10—*History*—A man, aged 76, had noticed marked palpitation after meals for about five years. Gradually increasing symptoms of hypertrophy of the prostate gland and retention had been observed for about three years previous to admission. The general examination was essentially negative, the prostate gland was found to be enlarged, and the condition of the urine and blood was that associated with urinary retention. The patient died suddenly while he was under observation.

Two small, firm, submucosal nodules, 2 mm in diameter were found in the ileum, at necropsy. The nodules were composed of the atypical basophilic polygonal or rounded epithelial cells characteristic of carcinoid tumors.

CASE 11—*History*—A man, aged 43, was attacked by a bull. He was brought to the hospital in a semicomatose condition and died soon after admission. A small, circumscribed, submucosal nodule was found in the ileum, at necropsy. On histologic examination the nodule was found to be composed of a few columns and masses of atypical polygonal, basophilic epithelial cells. The stroma was formed by a large amount of coarse connective tissue fibers and bundles of smooth muscle tissue.

STRUCTURE OF THE SMALL INTESTINE

The anatomy and general histology of the small intestine has been described by Jackson - Lewis and Bremer² Jordan³ and others

² Jackson C M in Morris Human Anatomy, ed 5 Philadelphia P Blakiston's Son & Company 1914, p 1161

³ Lewis F T and Bremer J L Text-Book of Histology Philadelphia P Blakiston's Son & Company 1927 p 256

⁴ Jordan H E A Text-Book of Histology, ed 3 New York D Appleton & Company 1924 p 363

Valuable contributions to the knowledge of the embryology of the small intestine have been made by Lewis,⁵ Eternod,⁶ Dandy,⁷ Mall,⁸ Berry,⁹ Carey¹⁰ and Johnson¹¹

The intestinal glands occur throughout the entire small and large intestines. They are simple tubules which extend the whole depth of the mucous membrane and open in the small intestines between the bases of the villi. The epithelium which lines the crypts of Lieberkühn consists of 3 main types of cells: goblet cells, columnar cells and cells first described by Paneth¹² that have a granular cytoplasm. The goblet cells resemble those present on the villi. The columnar cells in the deeper portions of the crypts are similar to those present on the sides of the villi. The columnar cells that line the neck of the crypts possess only an indistinct cuticular border. Mitotic figures are rather common among these cells. They are believed to be indifferent genetic cells which give rise to the various types of cells found in the intestinal glands or on the villi.

Schwalbe,¹³ in 1872, was apparently the first investigator to observe the granular cells present in the intestinal glands. In his examination of the intestinal tract of the rat he described in fresh material peculiar, coarsely granular cells occupying the deeper portions of the intestinal gland. Paneth, in 1888, described a peculiar type of granular cell situated in the fundus of the intestinal glands. They were found to be present in the intestines of mice, rats, cats, dogs and man. He compared them to the pancreatic cells and distinguished them definitely from the goblet cells.

5 Lewis, F. T. The Development of the Intestinal Tract and Respiratory Organs, in Keibel, Franz. Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2, p. 291.

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7 Dandy, W. E. A Human Embryo With Seven Pairs of Somites, *Am. J. Anat.* **10** 85, 1910.

8 Mall, F. P. Ueber die Entwicklung des menschlichen Darmes und seiner Lage beim Erwachsenen, *Arch. f. Anat. u. Entwicklungsgesch.* supp. 2, p. 403, 1897. Development of the Human Intestine and Its Position in the Adult. *Bull. Johns Hopkins Hosp.* **9** 197, 1898.

9 Berry, J. M. On the Development of the Villi of the Human Intestine. *Anat. Anz.* **17** 242, 1900.

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12 Paneth, Josef. Ueber die secernierenden Zellen des Dünndarmepithels. *Arch. f. mikr. Anat.* **31** 113, 1888.

13 Schwalbe, C. Beiträge zur Kenntnis der Drüsen in den Darmwandungen, insbesondere der Brunner'schen Drüsen. *Arch. f. mikr. Anat.* **8** 92, 1872.

Kultschitzky,¹⁴ in 1897, described a granular cell observed in the intestinal mucosa of dogs. The granules took a red color when stained by Ehrlich-Biondi solution. Since the granules took an acid stain, he named them "Zellen mit azidophilen Kernen." The intestinal tract of dogs on their usual diet contains a moderate number of these cells, they increase when the animals are put on an abundant meat diet and decrease in number and size on starvation. Schmidt,¹⁵ in 1905, described the presence of certain granular cells in the mucous membrane of the intestines of human beings. He fixed his material in Muller-formaldehyde solution. In both stained and unstained preparations, he observed peculiar cells which contained numerous yellow granules in their basal portions. He believed these cells to be of a different type from those described by Paneth and Kultschitzky. On the basis of the yellow granulation he called the cells "gelbe Zellen." Ciaccio¹⁶ shortly afterward described a special granular cell in the crypts of Lieberkuhn. The cells were investigated only in guinea-pigs and dogs. Besides the granules, numerous vacuoles were found in the cytoplasm. Klein¹⁷ examined the granule cells of the opossum and guinea-pig. He reached the conclusion that they are specific elements which secrete a special substance used during digestion. The granules were found to vary in size and shape. The smaller granules take a basic stain, and the larger, coarser granules are acidophilic.

Gosset and Masson¹⁸ restudied the granular cells of the intestinal mucosa. As a stain they used a solution of ammoniacal silver. In the deeper portions of the intestinal glands and in the region adjacent to the crypts, peculiar cells were found. Between the basement membrane and nucleus were numerous silver-staining granules of various sizes. The cells which contained these granules were called argentaffine cells. The cells were regarded as composing an endocrine gland of entodermal origin comparable to the islands of Langerhans of the pancreas. On proliferation the argentaffine cells formed an organoid tissue. The presence of silver-reducing cytoplasmic granules in the

14 Kultschitzky, N. Zur Frage über den Bau des Darmkanals, *Arch f mikr Anat* 49 7, 1897.

15 Schmidt, J. E. Beiträge zur normalen und pathologischen Histologie einiger Zellarten der Schleimhaut des menschlichen Darmkanals. *Arch f mikr Anat* 66 12, 1905.

16 Ciaccio, Carmelo. Sur une nouvelle espèce cellulaire dans les glandes de Lieberkuhn. *Compt rend Soc de biol* 60 76 (Jan 13) 1906.

17 Klein, Sidney. On the Nature of the Granule Cells of Paneth in the Intestinal Glands of Mammals. *Am J Anat* 5 315, 1906.

18 Gosset, A. and Masson, P. Tumeurs endocrines de l'appendice. *Presse med* 25 237 1914.

cells of the intestinal glands has been confirmed by Hasegawa,¹⁹ Damsch,²⁰ Sprafke²¹ and other investigators

Kull²² in the examination of the intestines of human beings, observed several types of granular cells. He classified these into (1) Paneth's cells, (2) cells with fine basal oxyphilic granules (the "acidophilen Zellen") and (3) cells with coarse yellowish basal granules (the "gelben Zellen" of Schmidt), which he considered as chromaffin cells.

Masson,²³ in 1924, investigated in detail the argentaffine cells of the appendix, but did not contribute new data. Cordier²⁴ found that the granule cells in the intestinal glands of guinea-pigs decreased or disappeared after the subcutaneous injection of pilocarpine hydrochloride. The granules in the pancreatic acini-like spaces were also diminished in number. In one hour and fifteen minutes after the injection, the granules had reappeared in the cells. The conclusion was reached that these cells have a secretory function similar to that of the pancreatic cells. Kull,²⁵ in a recent histologic and embryologic study of the granule cells of the intestinal tract, reached the conclusion that the granule cells are of mesodermal origin. Various color reactions of the granules in various cells are believed to be an index of development. Acidophilic granules are considered present only in young cells, whereas yellow granules are evidence of cell maturity. The size and number of the granules are a direct expression of the functional activity of the cells.

REVIEW OF THE LITERATURE

Carcinoid tumors of the small intestine usually appear as small circumscribed, firm nodules which project into the lumen. They are often multiple. The color varies with their size and tension on the superimposed mucosa. The larger nodules are yellow to grayish white. Their size varies from 3 mm to 1 cm or more in diameter. Their free surfaces are usually covered by the smooth normal mucosa, but

19 Hasegawa, Tomoo. Ueber die Carcinoide des Wurmfortsatzes und des Dunndarmes. *Arch f path Anat* **244** 8, 1923.

20 Damsch, Felix. Zur Histogenese der sogenannten Appendixkarzinoide. *Beitr z path Anat u z allg Path* **72** 687, 1923.

21 Sprafke, Hans. Untersuchungen über die argentaffinen Zellen in der Schleimhaut des Wurmfortsatzes und ihre Beziehungen zur Entstehung der sogenannten Karzinoide, Frankfurt. *Ztschr f Path* **35** 302, 1927.

22 Kull, Harry. Die "basal gekörnten Zellen" des Dunndarmepithels. *Arch f mikr Anat* **81** 185, 1913.

23 Masson, P. Appendicite neurogene et carcinoides. *Ann d'anat path* **1** 3, 1924.

24 Cordier, Robert. Contribution à l'étude de la cellule de Ciaracio-Masson et de la cellule de Paneth. *Compt rend Soc de biol* **88** 1227 (April 28) 1923.

25 Kull, Harry. Die chromaffinen Zellen des Verdauungs-tractes. *Ztschr f mikr-anat Forsch* **2** 163, 1925.

there may be superficial erosions or ulcerations which may produce irregular crater-like depressions. The primary nodules have the consistence of a hard fibroma. On section the surface is yellowish and firm. The histologic structure consists of irregularly arranged strands, columns and masses of peculiar polyhedral cells in an abundant, compact stroma of coarse collagenous fibers or bundles of smooth muscle.

Various names have been applied to carcinoid tumors of the small intestines. Many investigators, in their desire to emphasize a hypothetical histogenesis, have renamed these tumors. Langhans,²⁶ in 1867, described the first case as a polyp. Lubarsch,²⁷ in 1888, and Ransom,²⁸ in 1890, believed them to be atypical primary carcinomas and used the term carcinomata. Oberndorfer,²⁹ in 1907, was the first to use the term carcinoid to emphasize certain characteristics by which this tumor differed from true carcinoma. Bunting,³⁰ in 1904, Buickhardt,³¹ in 1909, and Krompecher,³² in 1919, used the term basal-cell carcinoma or basiloma to call attention to the morphologic resemblance of carcinoid tumors to basal cell carcinoma. Other recent terms are embryoma, by Primrose³³ in 1925, immature sympathetic neurocytomata, by Ehrlich³⁴ in 1914, argentaffine tumor, by Gosset and Masson³⁵ in 1914, endocrine tumor, by Masson³³ in 1924 and neurocine tumor, by Masson³⁵ in 1928.

Carcinoid tumors may occur anywhere in the gastro-intestinal tract. They are most common in the appendix and the small intestines. Saltykow³⁶ described tumors in the sigmoid and rectum composed of carcinoid cells.

26 Langhans, T. Ueber einen Drusenpolyp im Ileum, Arch f path Anat **38** 559, 1867.

27 Lubarsch, Otto. Ueber den primären Krebs des Ileum nebst Bemerkungen über das gleichzeitige Vorkommen von Krebs und Tuberculose, Virchows Arch f path Anat **111** 281, 1888.

28 Ransom, W. B. Primary Carcinoma of the Ileum, Lancet **2** 1020, 1890.

29 Oberndorfer, Siegfried. Ueber die "kleinen Dunndarmcarcinome," Verhandl d deutsch path Gesellsch **11** 113, 1907.

30 Bunting, C. H. Multiple Primary Carcinomata of the Ileum, Bull Johns Hopkins Hosp **15** 389 (Dec) 1904.

31 Buickhardt, J. L. Zur Lehre der kleinen Dunndarmkarzinome. Frankfurt Ztschr f Path **3** 593, 1909.

32 Krompecher, E. Über die Basalzellentumoren der Zylinderepithelschleimhäute mit besonderer Berücksichtigung der "Karcinoid" des Darms. Beitr z path Anat u z allg Path **65** 79, 1919.

33 Primrose, Alexander. Primary Carcinoma of the Small Intestine in an Octogenarian. Ann Surg **82** 429, 1925.

34 Ehrlich, S. L. quoted by Masson, P. Am J Path **4** 181, 1928.

35 Masson, P. Carcinoids (Argentaffin-Cell Tumors) and Nerve Hyperplasia of the Appendicular Mucosa. Am J Path **4** 181 (Mar) 1928.

36 Saltykow, S. Ueber die Genese der "Karcinoiden Tumoren" sowie der "Adenome" des Darmes. Beitr z path Anat u z allg Path **54** 550, 1912.

More than 104 cases of carcinoid tumors of the small intestines are reported in the literature. About 8 cases could not be considered on account of a meager or inconclusive description. A few reports of

Cases of Carcinoid Tumor of Small Intestines Reported in the Literature

Author	Year Reported	Metastasis to the Liver and Other Structures	Metastasis to the Lymph Nodes	Cases	Extension to the Serosa
Lamghans	1867			1	
Lubarsch	1888			2	
Ransom	1890	1		1	
Notthafft, <i>Deutsches Arch f klin Med</i> 74 557, 1895	1895			1	
Walter, <i>Arch f klin Chir</i> 53 1, 1896	1896			1	
Oberndorfer, <i>Beitr z path Anat u z allg Path</i> 29 519, 1901	1901			2	
Grawitz, <i>Deutsche med Wchnschr</i> 30 1794 (Dec 1) 1904	1904			1	
Bunting	1904			1	
Marekwald, <i>Munchen med Wchnschr</i> 1 1033 (May 30) 1905	1905			1	
Oberndorfer ²⁰	1907			7	
Trappe, <i>Frankfurt Ztschr f Path</i> 1 109, 1907	1907			1	
Verse, quoted by Burekhardt ³¹	1908		1*	3	2†
Verse, <i>Verhandl d deutsch path Gesellsch</i> 12 95, 1908	1908			6	
Burekhardt ³¹	1909			6	
Toennissen, <i>Ztschr f Krebsforsch</i> 8 354, 1910	1910			11	
Evstratoff, <i>Schweiz arztl Mitt u Univ Inst, Zurich</i> 7 301, 1911	1911	1		1	
Saltykow	1912		1‡	5	
Burekhardt, <i>Frankfurt Ztschr f Path</i> 11 219, 1912	1912			1	
Gruner and Fraser, <i>J Path & Bact</i> 17 165, 1912	1912			2	
Dietrich, <i>Frankfurt Ztschr f Path</i> 13 390, 1913	1913	1		1	
Schopper, <i>Verhandl d deutsch path Gesellsch</i> 16 387, 1913	1913	1		1	
Hageman, <i>Ztschr f Krebsforsch</i> 16 404, 1914	1917			10	
Judd, <i>Journal Lancet</i> 39 1-9 (April 1) 1919	1919			2	
Engel, <i>Ztschr f ang Anat</i> 7 385, 1920	1920		1	1	
Bakke, <i>Med Rev</i> 38 193, 1921	1921		1	1	
Schnitzel, <i>Arch f klin Chir</i> 124 652, 1923	1923	1		1	1
Hasegawa	1923			4	
Lauehe, <i>Virchows Arch f path Anat</i> 252 38, 1924	1924			2	
Primrose	1924			1	
Liu, <i>Arch Surg</i> 11 602 (Oct) 1925	1925		1	1	
Forbus, <i>Bull Johns Hopkins Hosp</i> 37 130, 1925	1925			2	
Stewart and Taylor, <i>J Path & Bact</i> 29 135, 1926	1926			1	
Dukes and Lockhart Mummery, <i>J Path & Bact</i> 29 308, 1926	1926	1		1	
Heine, <i>Deutsche Ztschr f Chir</i> 205 126, 1927	1927			1	
Huguier, <i>Paris chir</i> 19 38 (Jan) 1927	1927			1	
Windholz, <i>Frankfurt Ztschr f Path</i> 37 422, 1927	1927			1	
McGlannon and McCleary, <i>J A M A</i> 89 870 (Sept 10) 1927	1927			1	
Decker, <i>Rev med de la Suisse Rom</i> 48 143, 1928	1928		1	1	
Brocher, <i>Rev med de la Suisse Rom</i> 48 50, 1928	1928	1		1	
Semsroth, <i>Arch Path</i> 6 575 (Oct) 1928	1928			1	
Thibaudeau, <i>J Cancer Research</i> 13 66 (March) 1929	1929			1	
Oberndorfer, <i>In Handbuch der speziellen pathologischen Anatomie und Histologie</i> , Berlin, Julius Springer, 1929, vol 4, p 717	1929	1	4	13	—
Total		5	10	104	

* Case IX † Cases III and VII ‡ Case VII

cases were not available. The cases used as the basis for this summary are definite, microscopically proved cases of carcinoid tumors of the small intestines (table). They are composed of 21 malignant and 83 benign neoplasms.

For the sake of ready analysis, the 21 malignant cases will be considered in 3 groups. The first group includes 8 cases in which there was general metastasis, the second group includes 10 cases in which there was metastasis to the regional lymph nodes, and the third group consists of 3 cases in which the growth extended through the intestinal wall to involve the serosa.

The Malignant Lesions—In the twenty-one cases of malignant carcinoid tumor of the small intestine, the patients consisted of twelve men and eight women, in 1 case, the sex of the patient is not known. The patients between the ages of 30 and 40 consisted of one man and one woman, between 41 and 50, four men, between 51 and 60, five men and two women, between 61 and 70, one man and two women, between 71 and 80, one man and two women, and between 81 and 90, a woman. In one case the age of the patient is not known. The average age in the twenty malignant cases was 57.2 years, the average age for the men was 53.2 years, and for the women 61.3 years.

The primary lesion was in the ileum in all 21 cases, it was in the upper portion in 3 cases, in the middle portion in 1 case, and in the lower portion in 17 cases. Four of these 17 tumors were within 10 cm. of the ileocecal valve. The smallest primary lesion was 5 mm. in diameter, and the largest 4 cm. in diameter.

In 17 cases the primary growth was nodular, in 4 cases it was annular. The primary lesion was multiple in 8 cases and single in 11 cases. In 4 cases in which the number of multiple nodules was recorded they numbered 14, 2, 14, and 10. In 10 cases there were symptoms and signs typical of obstruction in the small intestine. In 2 cases there were indefinite complaints of cachexia and anemia.

The Benign Lesions—In 83 cases regional or distal metastasis was not found. The neoplasm did not involve the serosa. This group will be considered as benign to distinguish it from the previously described group in which metastasis had occurred. The amount of published data varies considerably in the different reports. This summary cannot, therefore, include every case in the consideration of the various factors. In 73 cases, the patients included 38 men and 35 women.

The age distribution in 68 cases (forty men and twenty-nine women) was as follows. The youngest man was aged 33 and the youngest woman 20, the oldest man was 86 and the oldest woman 79. The average age in 68 cases was 54.3 years, the average age for the twenty-eight women 47 years and for the forty men 58.8 years. The patients between the ages of 20 and 30 included five women, between 31 and 40 three men and seven women, between 41 and 50 six men and four women, between 51 and 60 eleven men and three

women, between 61 and 70, ten men and seven women, between 71 and 80, seven men and one woman, and between 81 and 90, three men and one woman

In 71 cases, the lesion was situated as follows in the duodenum in 2 cases, in the upper portion in 1 case, and the site was not designated in 1 case, it was situated in the jejunum in 11 cases, and in the ileum in 58 cases, in the upper portion in 7 cases, in the middle portion in 5 cases, in the lower portion in 44 cases and in the tip of a Meckel's diverticulum in 2 cases

The number of nodules varied from 1 to 33 in 76 cases, single nodules occurred in 49 cases, and multiple nodules were found in 27 cases. In the 27 cases there were from 1 to 5 nodules in 16 cases, from 6 to 10 nodules in 3 cases, 24 nodules in 1 case, 33 nodules in 1 case and multiple nodules, but the number was not given, in 6 cases. The lesions were nodular in 62 of 63 cases and ring-shaped in 1. The size of the nodules varied from 1 mm to 2.5 cm in diameter. The usual diameter was from 3 to 8 mm.

Of the 83 cases, 6 were discovered at exploratory operation and 75 at necropsy, in 2 cases these data are absent. The symptoms in the 6 cases were typical of intestinal obstruction.

Histogenesis—The histogenesis of carcinoid tumors has been a subject of much discussion during the last thirty years. There are many factors that have stimulated continuous interest in this group of tumors. It is sufficient to call attention to a few, such as the atypical cytologic manifestations, small size, unusual distribution, multiplicity and variable clinical course. Many cell types from all germ layers and a number of embryonic anomalies have been considered as the origin of the tumor. Although much intensive work has been done, a theory of histogenesis has not been generally accepted. The application of the chrome fixatives and silver stains in the differentiation of the cells, however, has resulted in considerable elucidation of this problem.

The various conceptions of the origin of the tumor will first be tabulated for easy reference, and then considered in detail.

I Cells which form the crypts of Lieberkuhn

1 Cell type not designated³⁷

2 Cell similar to the basal cells of the epidermis³⁸

37 Langhans (footnote 26) Lubarsch (footnote 27) Walter, Maximilian Ueber das multiple Auftreten primären bösartigen Neoplasmen Arch f klin Chir **53** 1, 1896 Gruner, O C, and Fraser, J R Primary Carcinoma of the Ileum J Path & Bact **17** 165, 1912 Schopper, K I Ueber ein "kleines Dunndarmkarzinom" mit ausgedehnter Metastasebildung, Verhandl d deutsch path Gesellsch **16** 387, 1913

38 Bunting (footnote 30) Krompecher (footnote 32) Burckhardt, J L Ueber das kleine Dunndarm- und Appendix-Karzinom, Frankfurt Ztschr f Path **11** 219, 1912

- 3 Granular cells
 - (a) Paneth's cells ³⁹
 - (b) Chromaffin cells ⁴⁰
 - (c) Argentaffine cells ⁴¹
- II Pancreatic tissue
 - 1 Pancreatic tissue displaced during fetal life ⁴²
 - 2 Pancreatic tissue (islands of Langerhans ⁴³)
- III Sympathetic nervous system
 - 1 Cells of the celiac ganglia ²⁰
 - 2 Cells of Auerbach's plexus ⁴⁴
- IV Embryonic maldevelopments
 - 1 Embryonic remnants of the ductus omphalomesentericus ⁴⁵
 - 2 Embryonic epithelial rests ⁴⁵
 - 3 Embryonic heterotopic tissue ⁴⁶
 - 4 Faulty differentiation of the entoderm ⁴⁷

The peculiar morphologic appearance of the characteristic cells that compose carcinoid tumors impressed even the earliest observers. The microscopic distinction from adenocarcinoma of the small intestine is

39 Huebschmann, P. Sur le carcinome primitif de l'appendice vermiculaire, *Rev med de la Suisse Rom* **30** 317, 1910

40 Dukes, Cuthbert, and Lockhart-Mummery, P. Carcinoid Tumour of the Ileum with Metastases, *J Path & Bact* **29** 308, 1926. McGlannon, Alexis, and McCleary, Standish. Carcinoid Tumors of the Small Intestines, *J A M A* **89** 850 (Sept 10) 1927. Huebschmann (footnote 39)

41 Gosset and Masson (footnote 18). Hasegawa (footnote 19). Sprafke (footnote 21). Masson (footnotes 23 and 35). Forbus, W. D. Argentaffine Tumors of the Appendix and Small Intestine, *Bull Johns Hopkins Hosp* **37** 130, 1925

42 Trappe, Max. Ueber geschwulstartige Fehlbildungen von Niere, Milz, Haut und Darm, *Frankfurt Ztschr f Path* **1** 109, 1907. Dietrich, A. Kleine Darmkarzinome von Typus der Karzinoide mit schwerer Leberkarzinose, *Frankfurt Ztschr f Path* **13** 390, 1913. Oberndorfer, Siegfried. Die Geschwulste des Darmes, in *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1929, vol 4, p 717. Heller, A. Discussion, *Verhandl d deutsch path Gesellsch* **11** 115, 1907

43 Saltykow (footnote 36). Lauche, Arnold. Die Heterotopien des ortsgelagerten Epithels im Bereich des Verdauungskanal, *Virchows Arch f path Anat* **252** 38, 1924

44 Marchand, F. Discussion, *Verhandl d deutsch path Gesellsch* **11** 115, 1907. Sternberg, C. Discussion, *Verhandl d deutsch path Gesellsch* **11** 116, 1907

45 Toennissen, E. Untersuchungen über die in der Submukosa des Dünndarms vorkommenden epithelialen Tumoren, *Ztschr f Krebsforsch* **8** 354, 1910. Borrmann, R. Discussion, *Verhandl d deutsch path Gesellsch* **11** 116, 1907

46 Hagemin, F. Ueber die Beziehungen der sogenannten Karzinoide des Darmes zu den Darmkrebsen, *Ztschr f Krebsforsch* **16** 404, 1917

47 Semroth, Kurt. The Histogenetic Interpretation of Certain Carcinoids of the Small Intestines, *Arch Path* **6** 575 (Oct) 1928

easy and definite Langhans, who first described the carcinoid tumors of the small intestine, emphasized the unusual appearance of the polyhedral cells. It was his belief that the origin of the cells was directly from the epithelial cells of the crypts of Lieberkuhn. Lubarsch described the arrangement of the cells in nests and strands. He emphasized the dissimilarity between the cells that composed these tumors and the cells that formed ordinary adenocarcinoma. He demonstrated by serial sections direct connection between the strands of carcinoid cells and the crypts of Lieberkuhn. He concluded that the tumors differed from adenocarcinoma or any other previously described neoplasm of the gastro-intestinal tract. As the basis for this distinction, he called attention to the multiplicity of the tumor, lack of metastasis, absence of true glands, gross appearance and peculiar structure of the individual cells. The epithelial cells of the glands of Lieberkuhn were believed to be the type cell. By calling the tumor "primary carcinoma of the ileum," he failed to impress the distinction from adenocarcinoma which he had made. The majority of observers during the next ten years⁴⁸ accepted Lubarsch's histogenic conception. Bunting in 1904, Buickhardt in 1909, and Krompecher in 1919, suggested, on account of the morphologic resemblance, that carcinoid tumors were similar to basal cell carcinoma.

Krompecher³² suggested that the basal cells of Lieberkuhn's crypts can differentiate into any of three types of basal cell carcinoma. These types he designated as solid, cystic and adenomatous basal cell carcinoma. He did not furnish any report of a case of carcinoid tumor.

Huebschmann, in 1910, in his study of carcinoid tumors of the appendix, made the suggestion that on account of the yellow color of these neoplasms they originated from Paneth's cells or from the chromaffin cells. He did not use chromic acid as a fixative. McGlannon and McCleary examined a carcinoid tumor that they believed to originate from the chromaffin cells at the base of the crypts of Lieberkuhn. The cytoplasmic granules gave a definite argentaffine reaction. Dukes and Lockhart-Mummery, in a thorough histologic study, reached the same conclusions.

Gosset and Masson, in 1914, studied the chromaffin cells of the intestinal tract, and were the first to show that cytoplasmic granules present in certain cells situated at the base of the crypts of Lieberkuhn reduced an ammoniacal solution of silver salts. The granules were stained black. A new nomenclature was suggested by this reaction. The granules were called argentaffine granules, the cells in which the

48 Notthafft A. Ueber die Entstehung der Carcinome *Deutsches Arch. f. klin. Med.* 54 555, 1895. Walter (footnote 37 third reference). Gruner and Fraser (footnote 37, fourth reference). Schopper (footnote 37 fifth reference).

granules were found, argentaffine cells, and tumors which were partly or wholly formed by these cells, argentaffine tumors. Significant observations were made on the argentaffine cells. They were found in the deeper portions of the crypts of Lieberkuhn throughout the entire gastro-intestinal tract. Most of them were found between the cylindric cells of the mucosa, but an occasional cell was not in direct contact with the lumen. The cells were believed to form an endocrine gland of endodermic origin similar to the islands of Langerhans. On proliferation of certain argentaffine (neurocrine) cells, a tissue was formed which was believed to possess an organoid character. Danisch, Hasegawa, and Forbus substantiated the presence of argentaffine cells in the crypts of Lieberkuhn. Forbus used the argentaffine reaction as a means of distinguishing carcinoid tumors of the small intestine from other growths. He was of the opinion that unless the cells of a morphologically carcinoid tumor show the argentaffine reaction, it should be considered as an adenocarcinoma. By this means he suggested the possibility of differentiating a third group of epithelial intestinal neoplasms which has the microscopic morphology of carcinoid tumor but the clinical course of adenocarcinoma. Hasegawa concluded that carcinoid tumors of the small intestines may arise in three different ways: (1) directly from the principal cells of the crypts of Lieberkuhn, (2) from the chromaffin cells and (3) from the submucous epithelial rests. Masson,⁴⁹ in his later work based on the study of fifty carcinoid tumors from the appendix, concluded that the argentaffine cells migrate from the crypts of Lieberkuhn into the submucosa. Here the cells invade a mass of subglandular nonmedullated nerve fibers. In this situation, the cells may differentiate into any 1 of 4 types: (1) cylindrical, (2) ganglionic, (3) resembling Schwann's and (4) neurocrine. Carcinoid tumors originate by autonomous amitotic division of the neurocrine cells. On proliferation, the neurocrine cells rupture the nerve sheaths and extend into the submucosa.

Danisch, on the basis of embryologic observations, came to a somewhat different conclusion. He observed that argentaffine cells do not appear in the crypts of Lieberkuhn until the fourth fetal month. He did, however, see the argentaffine cells in the submucosal connective tissue of the intestines in an 11.5 cm human embryo. Here the argentaffine cells were not in relation to the already well developed crypts of Lieberkuhn, but were situated as individual cells in the loose connective tissue. The cells were believed to migrate from the connective tissue into the crypts of Lieberkuhn. By studies on the chick embryo, he found that argentaffine cells first appear in the celiac ganglion. He concluded that argentaffine cells originating in the celiac ganglion migrated

⁴⁹ Masson (footnotes 23 and 35)

along the nerve fibers into the submucosa and eventually reached the crypts of Lieberkuhn. If argentaffine cells remained about Meissner's ganglions or in the submucosa, they could form carcinoid tumors. The origin of carcinoid neoplasms is thus paraganglionic, from the celiac ganglion of the sympathetic system. Masson³⁵ and Danisch agreed that the type cell of carcinoid tumors is from argentaffine cells present in the submucosa. Masson,⁴⁹ however, suggested the crypts of Lieberkuhn or the endoderm, and Danisch pointed out the chromaffin cells of the sympathetic ganglion or the ectoderm as the actual source of the argentaffine cells.

Ehrlich stated that carcinoid tumors arise from Auerbach's plexus. The tumor cells would thus originate from sympathetic nerve cells. He designated the tumors as immature sympathetic neurocytomata.

Oberndorfer, in 1907,⁵⁰ presented his work on carcinoid tumors of the small intestine, based on the examination of 6 cases of benign tumors. He directed attention to several characteristics of these tumors which have become widely accepted. The tumors were described as small, usually multiple, circumscribed, submucosal, noninfiltrating, benign masses of undifferentiated cells. To distinguish the clinical course from that of carcinoma, he suggested the name carcinoid tumor. A definite statement was not made as to the origin, but he seemed to favor the possibility that they are derived from pancreatic rests. Trappe, in 1907, suggested that rests of pancreatic tissue are common in the gastro-intestinal tract. These rests were considered by him to be the source of carcinoid tumors and adenomyomas of the small intestine. Heller and Albrecht⁵¹ supported the opinion of Trappe.

Saltykow developed the ideas of Trappe still further. He expressed the belief that carcinoid tumors originate from rests composed entirely of islands of Langerhans. Lauche also considered this to be the most plausible explanation of their true nature.

Marchand and Sternberg expressed the belief that the carcinoid tumor develops from cellular remnants of the ductus omphalomesentericus.

Embryonic epithelial rests were first suggested as the origin of carcinoid tumors by Boirmann. Toenniessen considered them not only as derived from submucosal epithelial rests, but suggested that they might function as glands of internal secretion. The similarity of the carcinoid cells and the cells of the islands of Langerhans was emphasized by him as additional proof.

50 Oberndorfer (footnote 42, third reference)

51 Albrecht, H. Discussion, Verhandl d deutsch path Gesellsch 11 115
1907

Hageman presented in considerable detail his conception of the development of carcinoid tumors from embryonic heterotopic tissue present in the intestinal wall

Semsioth, in 1928, suggested that carcinoid tumors in the duodenum develop as the result of dysontogenetic heterotopy. This conclusion was reached on the observations in one case in which there was no sign of malignancy, but evidence of dysotogenesis in the form of pancreatic tissue in the duodenum. Kull²⁵ expressed the belief that the argentaffine cells originate from cells in the submucosa which migrate into the crypts of Lieberkuhn. This conception of the origin of the argentaffine cells suggests a possible mesodermal type cell to be the progenitor of carcinoid tumors.

In summarizing the conception of the histogenesis of carcinoid tumors, it is apparent that at present there are a number of possibilities, none of which can be considered as proved or established. The origin of carcinoid tumors has been assigned to the principal epithelial cells of the crypts of Lieberkuhn, to Paneth's cells and to the basal granular cells (chromaffin cells). They have been considered malformations developing from pancreatic rests or accessory pancreas, and finally as fetal epithelial rests or remnants of the ductus omphalomesentericus.

COMPARISON WITH BASAL CELL CARCINOMA OF THE SKIN

There are certain resemblances between carcinoid tumors of the small intestine and basal cell carcinoma of the skin that have led some investigators to believe that these tumors are related.³¹ The cells of both tumors take a basic stain, they tend to grow in solid sheets or cords and do not show cell boundaries. The benign clinical course of both was emphasized before it was recognized that many carcinoid tumors of the intestine form metastasis. However, a close histologic study revealed wide differences in structure. Basal cell carcinomas frequently show a few cornified cells, and they never give the argentaffine reaction. In 268 cases of basal cell carcinoma, Broders⁵² did not find metastasis beyond the regional nodes.

COMPARISON WITH CARCINOID TUMORS OF THE VERMIFORM APPENDIX

Selinger stated that the first case of authentic carcinoid tumor of the appendix was reported by Begei⁵³ in 1882. Up to 1906 only 42

⁵² Broders, A. C. Basal-Cell Epithelioma, J. A. M. A. **72** 856 (March 22) 1919.

⁵³ Begei, A. Ein Fall von Krebs des Wurmfortsatzes, Berl. klin. Wchnschr. **19** 616 (Oct.) 1882.

cases had been reported Simon,⁵⁴ in 1916, in a careful examination of the literature, found 325 cases of epithelial tumors of the appendix. After excluding all cases of apparent adenocarcinoma and doubtful cases, he concluded that 260 were of definite carcinoid type. Van Alstine⁵⁵ reviewed 300 cases in 1926, and Oberndorfer, in 1929, described 29 cases observed in his own laboratory.

Carcinoid tumors of the appendix are more common than carcinoid tumors of the small intestines. Warwick⁵⁶ found in statistics of 29,320 appendices removed at operation, that in 82 (0.28 per cent) carcinomatous tumors were present. Kennedy⁵⁷ examined 350 appendices removed at necropsy, but found only one case (0.28 per cent) of carcinoma. In a study of 41,838 necropsies, Maydl and Nothnagel⁵⁸ observed 2 cases of carcinoma of the appendix. Reimann⁵⁹ found 17 cases of carcinoma on examination of 13,151 appendices removed at operation. Three of the 17 cases were of the columnar cell type whereas 14 (82 per cent) were carcinoid in structure. MacCarty and McGrath,⁶⁰ in the examination of 8,039 appendices as a routine, found 40 cases of carcinoma.

MacCarty and McGrath noted that the average age of the 40 patients with carcinoma of the appendix was 30 years. Oberndorfer⁵⁰ reported that in 11 cases of carcinoid tumors discovered at necropsy the average age was 57 years, whereas in 18 cases discovered in surgically removed specimens the average age was 24 years. In 66 per cent of 186 cases of carcinoid tumors of the appendix Simon found that the patients were less than 30 years. Selinger⁶¹ found that the average age of the patients in 34 cases of primary carcinoma of the appendix was 34 years.

The majority of reported cases has occurred in women. MacCarty and McGrath found 24 per cent in males and 76 per cent in females, Selinger found 17.6 per cent in males and 82.4 per cent in females, Simon found 34.9 per cent in males and 65.1 per cent in females, and Oberndorfer⁵⁰ found 29 per cent in males and 61 per cent in females.

54 Simon, W. V. Das Karzinom und das Karzinoid der Appendix mit einem kurzen Überblick auch über die übrigen an der Appendix vorkommenden Tumoren, *Ergebn d. Chir. u. Orthop.* **9**: 291, 1916.

55 Van Alstine, G. S. Primary Carcinoma of the Appendix. Report of Two Cases with Brief Review of the Literature, *Illinois M. J.* **49**: 469 (June) 1926.

56 Warwick, Margaret. Primary Carcinoma of the Appendix. *Minnesota Med J.* **5**: 512, 1922.

57 Kennedy, A. M. Primary Carcinoma of Appendix, *Lancet* **2**: 1757, 1910.

58 Maydl and Nothnagel, quoted by Whipple, T. R. C. *Lancet* **1**: 319, 1901.

59 Reimann, S. P. Primary Carcinoma of the Vermiform Appendix, *Am. J. M. Sc.* **156**: 190, 1918.

60 MacCarty, W. C., and McGrath, B. F. The Frequency of Carcinoma of the Appendix. *Ann. Surg.* **59**: 675, 1914.

61 Selinger, J. Primary Carcinoma of the Vermiform Appendix. *Ann. Surg.* **89**: 276 (Feb.) 1929.

Carcinoid tumors of the appendix are most commonly situated in its distal third. Simon found 139 cases distributed as follows: in the distal third, 77 per cent; in the middle third, 14 per cent; in the upper third, 7 per cent; and in the entire organ, 2 per cent.

MacCarty and McGrath found in 40 cases that 90 per cent were situated at the tip. Reimann stated that in 17 cases of carcinoma of the appendix, "practically all of the tumors were situated at the tip or in the distal third. A bulbous tip was exhibited by four." Selinger described the situation of the lesion in 34 cases as follows: "twenty at the tip, five at the base, one midway between tip and base."

Carcinoid tumors of the appendix consist almost always of a single nodule. Simon stated that only 5 cases of multiple carcinoid tumors of the appendix had been reported up to 1916. The tumor produces nodular bulging of the appendix, but many tumors cannot be detected except by section of the entire appendix. The tumor varies from a microscopic lesion to a growth 2 cm. in diameter. The serosa is smooth and shiny over the nodule. When the nodule reaches sufficient size it projects into the lumen, producing partial or complete obliteration. On section, the carcinoid tumor may be yellowish gray, but it is frequently grayish white. It usually forms a small, hard, single, submucosal nodule. On section, it is found to be covered by the mucosa. MacCarty and McGrath found in 28 cases that the nodules were palpable on the exterior only in 5, the other 23 were discovered on gross section, carried out as a routine.

The microscopic examination of a carcinoid tumor of the appendix usually shows a small, compact, submucosal nodule. It seldom infiltrates the muscularis but may erode the mucosa. The main portion of the mass consists of cords, sheets or irregularly arranged atypical epithelial cells. The cells are round, oval or polyhedral. In the peripheral portions of the larger masses they assume a cubical appearance. The cells are definitely smaller than the columnar cells of the appendix and have no resemblance to the mucous cells. The cytoplasm is sparse and somewhat pale. It is frequently homogeneous but vacuoles and fat globules may occur. The nucleus is prominent. It is round or oval and takes a deep basal stain on account of an abundant content of chromatin. Chromatin granules, as well as a fine network of chromatin threads, may occasionally be distinguished.

The cells are sometimes grouped about a space in such a manner as to suggest a vesicular or alveolar arrangement. The contents of spaces are stained a pale red by eosin. The stroma may vary from a few loose connective tissue fibers to an abundant deposition of coarse collagenous or hyaline sheets of connective tissue. Bundles of muscle cells are often a portion of the stroma. When the columns of cells invade

the muscular layers, they may be isolated among bundles of smooth muscle. Lymphocytes may be found about the masses of carcinoid cells, but they are usually absent. The epithelial cells contain cytoplasmic granules which reduce an ammoniacal solution of silver. When fixed in solutions of chrome salts, the granules take a yellow color. In some carcinoid tumors of the appendix, anisotropic cytoplasmic granules or spherules have been described. The presence of silver or of argentaffine granules is considered a specific histochemical test for the identification of the carcinoid cell. Spiafke, however, recently showed that two carcinoid tumors examined by him did not contain any argentaffine cells.

The histogenesis of carcinoid tumors of the appendix is believed to be identical with carcinoid tumors of the small intestine. All important conceptions have been previously considered and need not be reconsidered.

The clinical course depends somewhat on the situation and size of the tumor. It may produce symptoms similar to those usually interpreted as chronic or mild recurrent appendicitis. Carcinoid tumors of the appendix which metastasized to the regional lymph nodes have been described by Hasegawa and Oberndorfer⁶². General metastasis has not been produced by a carcinoid tumor of the appendix.

A histologic study was made of 5 cases of carcinoid tumor of the appendix. The structure of these tumors indicates that morphologically they are closely similar to, if not identical with, carcinoid tumors of the small intestine. However, in the case of carcinoid tumors of the appendix, distant metastasis has not been described, and metastasis in the lymph nodes is extremely rare.

COMMENT

Only 9 cases of carcinoid tumors of the small intestine had been observed when Oberndorfer,⁶² in 1907, presented his observations on 7 cases. On the morphologic and clinical evidence in this group of entirely benign tumors, he defined carcinoid tumors of the small intestine as small, usually multiple, submucosal, hard, grayish-white nodules usually situated in the ileum. The definition was appropriate at the time on the basis of the material observed, but the conception that carcinoid tumors of the small intestine are benign has remained, and is a general belief even at present. It seems to me that the definition of carcinoid tumors must express the significant fact that they may grow to a large size and produce intestinal obstruction, and that metastasis has occurred in more than 20 per cent of all cases reported.

⁶² Oberndorfer, Siegfried. *Karzinoid Tumoren des Dünndarms*, Frankfurt Ztschr. f. Path. 1 426, 1907.

Few tumors have been given so many different names to designate their structure, clinical course and origin. Many investigators have been anxious to use a term that would express a specific derivation. Since 1910, the term carcinoid tumor of the small intestine has been used almost universally. Recent workers in this field still use the term carcinoid tumors even while simultaneously suggesting a new name.

Carcinoid tumors of the small intestine are not common. Only 2 cases in which the tumor was considered malignant have been observed in 12,000 necropsies performed in the department of pathology of the University of Minnesota. However, more than 104 cases have been reported in the literature. In about 20 per cent of all reported cases, metastasis has occurred. It may be that more cases have been observed, but only those reports were published which appeared to be of clinical interest. Many cases have been reported from a small number of German laboratories. Oberndorfer,⁵⁰ 20 cases, Toennissen, 11 cases, Buckhardt,³¹ 7 cases, and Hageman, 10 cases. This may be interpreted in two ways, either that the tumor does not occur at other places with the same frequency, or that it is not looked for at necropsy. The knowledge of this tumor has been based principally on the observation of single cases. So far as I know, my summary includes all authentic cases in the available literature. The summary begins with the first case published by Langhans in 1867, and includes the cases reported up to October, 1929. More than 104 cases of carcinoid tumors of the small intestine have been reported. Although certainly not common, it should be considered as a possible cause in obstruction of the small intestine, especially if the obstruction can be localized in the distal portion of the ileum.

A carcinoid tumor is usually considered to be small. In the 21 malignant lesions, the smallest lesion was 5 mm and the largest 4.5 cm in diameter, whereas in 83 benign lesions, the smallest lesion measured 1 mm and the largest 2.5 cm in diameter. The average size is from 5 mm to 1 cm in diameter. It is well to remember that by a consideration of size alone, it is impossible to differentiate this tumor from adenocarcinoma.

Since Lubarsch described his 2 cases of carcinoid tumors of the small intestine, the conception that the tumor is multiple has become firmly fixed as a general conception. But in the entire group of 104 cases the tumor was multiple in only 35 cases and single in 60 of 95 cases in which this information was available. In the group of 21 cases in which the tumor was malignant it was multiple in 8 cases and single in 11 cases. In the group of 60 cases in which the tumor was benign, the tumors were multiple in 27 cases and single in 49 cases. There was no definite relation of the number of nodules, the site, the age of the patient or the incidence of metastasis.

A determination of the most common site of the primary lesion of the carcinoid tumors in the small intestine is of importance to the pathologist and clinician. In 92 cases, the primary lesion was found in the duodenum in 2, in the jejunum in 11 and in the ileum in 79. The apparent predilection of this tumor for the ileum becomes more pronounced if one takes into consideration only the group in which the malignant changes were present. Twenty-one malignant lesions occurred in the ileum, and of these, 17 were in the distal third. In the group of 71 benign lesions, 58 were in the ileum, and 44 of these were in the distal third. In 2 cases the lesion was at the tip of a Meckel's diverticulum.

Although the primary lesion in the majority of reported cases has been nodular, in 5 of 84 cases it was annular. Four of the 5 annular lesions were found in the group of 21 malignant lesions.

None of the numerous suggestions advanced to explain the histogenesis of carcinoid tumors of the small intestine has received unanimous confirmation. The problem has been approached from many angles and by a number of ingenious methods. Parat,⁶³ Masson,²³ Dietrich, Kull²⁵ and others have made detailed embryologic studies in this field. Their conclusions do not agree. Parat and Masson²³ traced the type cell to the endoderm, Dietrich to the ectoderm and Kull to the mesoderm. Further information appears to be essential for the clarification of these contradictory conclusions.

The morphologic studies can be considered in two periods: before the application of stains which showed the intracellular granules and after the application of specific granular stains. During the first period the principal epithelial cells of the crypts of Lieberkuhn or embryologic anomalies were considered as the source of carcinoid tumors of the small intestine. It is evident that the peculiar morphology and staining qualities of the cells were appreciated and by these qualities definitely distinguished from adenocarcinoma by Lubarsch in 1888. Bunting, in 1904, made a distinct contribution when he emphasized the resemblance of the cells to those which form basal cell carcinoma of the skin.

There are few supporters of the numerous hypotheses of the origin of carcinoid tumors from embryologic malformations, displacements or arrested development. The suggestion by Huebschmann that carcinoid tumors originate from the chromaffin cells of Kultschitzky directed attention to a new approach to the investigation of this neoplasm. Credit should also be given to Oberndorfer,²⁹ who, in 1907, reported 7 cases of carcinoid tumor of the small intestines and observed that the tumor

⁶³ Parat M. Contribution a l'histophysiologie des organes digestifs de l'embryon, *Compt rend Soc de biol* 90 1023 (April 18) 1924.

takes a yellow stain when fixed in a solution of chromic acid and formaldehyde Huebschmann, on the other hand had not observed a case, and did not apply his idea Numerous workers since 1914 have applied special stains to demonstrate the acid granules, chromaffin granules or argentaffine granules in the cytoplasm of the cells which form carcinoid tumors The present conception of the basal granule cell is that reached by Kull, in 1925, who expressed the belief that the granules in the basal granule cell may take a chromaffin, acid or silver stain In other words, this is a single cell type The granules may, however, take various stains when in different functional stages The detailed work of Masson³⁵ and Danisch must be carefully investigated and confirmed on a larger scale No explanation of the histogenesis of carcinoid tumors of the small intestine presented up to the present time can be accepted without reservation

The clinical significance of carcinoid tumors has not been correctly estimated or understood The condition has not been diagnosed before operation or necropsy This may be due to the false conception of this tumor as always small, uncommon and benign Another factor is the absence of a summary of the reported cases In an analysis of the data it seems advisable to consider separately the group of 21 cases of malignant tumor and the 83 cases of benign tumor In the group of 21 cases, there were definite evidences of intestinal obstruction in 10 The symptoms were nausea vomiting, constipation with or without intermittent diarrhea, abdominal pain loss of weight, cachexia palpable abdominal tumor and enlargement of the liver In one case the main complaint was cachexia and in another severe anemia The chief clinical picture is that associated with obstruction of the small intestine, and it is found in about 50 per cent of the malignant cases In the group of 83 benign cases clinical evidences of a lesion were present in only 6 The symptoms and signs in 4 cases were similar to those in the malignant group which produced obstruction of the intestinal lumen In 2 cases the symptoms and signs were suggestive of appendicitis

There is cytologic similarity between carcinoid tumors of the small intestine and carcinoid tumor of the appendix This morphologic resemblance has been considered sufficient basis for considering the 2 groups not only similar but identical Bunting Burckhardt³⁶ and Krompecher expressed the belief that carcinoid tumors are basal cell carcinomas of the gastro-intestinal tract Krompecher in a study of this question not only reached this conclusion but subdivided carcinoid tumors into three groups dependent on the arrangement of the cells

Similarities and differences in the clinical course of adenocarcinoma of the small intestine basal cell carcinoma of the skin carcinoid tumors

of the small intestine and carcinoid tumors of the appendix may be considered briefly. The malignant nature and metastatic tendencies of adenocarcinoma have recently been emphasized by Hellstrom⁶⁴. He analyzed 70 cases from the literature and added 3 of his own in which resection had been performed for intestinal obstruction. The usual features of this neoplasm are too well known to be considered. Intestinal obstruction is usually the predominant symptom. Metastasis occurs early. In basal cell carcinoma of the skin, the opposite condition holds true. The age of the patient is usually more than 50 years, and the duration of the lesion from one to several years. The primary lesion is nearly always single, most lesions occur on the exposed portion of the skin, and metastasis is exceedingly rare. Only a few cases have been reported in which the tumor involved the regional lymph nodes. General metastasis has not been observed in any case. Carcinoid tumors of the appendix discovered in surgically removed specimens usually occur in persons less than 35 years of age. The symptoms produced are those of what is commonly called chronic appendicitis. In all proved cases of carcinoid tumor of the appendix, metastasis has not progressed beyond the regional lymph nodes. When a tumor of the small intestine is observed on roentgenoscopic examination or is found on exploratory laparotomy, it is essential to consider the possibility of a carcinoid tumor. It is not possible to make a differential diagnosis from an adenocarcinoma by physical signs or symptoms. A multiple tumor in the ileum strongly suggests a carcinoid tumor. All tumors of the small intestine, regardless of number, size, shape or distribution, should be examined microscopically for a correct pathologic diagnosis. The surgical procedure, and certainly the prognosis, will be influenced by the correct histologic interpretation.

The prognosis after removal of carcinoid tumors of the small intestine is favorable in the absence of metastasis. The fact must be recognized that metastasis occurred in 21 of 104 reported cases. In 38 per cent of 21 cases, general metastasis was present.

The only treatment for carcinoid tumors is surgical removal. This is essential when the primary tumor has reached more than 1 cm in diameter. The primary tumor in all cases in which it was malignant was about this size or larger. If obstruction is produced, removal becomes imperative. The favorable prognosis after surgical removal in the cases reported by Decker, Bakke and Primrose should be noted.

⁶⁴ Hellstrom, John. Primary Carcinoma in Jejunum and Ileum. *Acta chirurg. Scandinav.* 62: 465, 1927.

SUMMARY

Eleven additional cases of carcinoid tumor of the small intestine are reported, 3 of which were malignant and 8 of which were benign. Intestinal obstruction was caused by 3 of the malignant and 1 of the benign tumors. Five cases occurred in the seventh decade. The primary lesion was a single circumscribed nodule in 7 cases, multiple nodules in 3 cases and an annular constriction in 1 case. The primary lesion was in the jejunum in 2 cases and in the ileum in 9 cases. The size of the lesions varied from 0.2 cm. to 2 cm. in diameter.

In the available literature, there are reports of 21 malignant and 83 benign carcinoid tumors of the small intestine. The liver was involved in 8 cases, the regional lymph nodes in 11 cases and the serosa of the intestine in 3 cases. In 10 of 21 cases of malignant tumor and in 6 of 83 cases of benign tumor, the tumor produced intestinal obstruction. The primary lesion may be in the duodenum, jejunum or Meckel's diverticulum, but is most commonly situated in the distal portion of the ileum. The lesion is often multiple, but usually it is single. The largest number occurs in the fifth and sixth decades. There is no special predominance in either sex.

The histologic picture of carcinoid tumors of the small intestine suggests benign tumor, but metastasis occurs in about 20 per cent of the reported cases.

EXPERIMENTAL SHOCK

VI THE PROBABLE CAUSE FOR THE REDUCTION IN THE BLOOD PRESSURE FOLLOWING MILD TRAUMA TO AN EXTREMITY †

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In a recent communication,¹ the results of experiments in which the blood pressure was reduced to a low level in short periods of time were reported. The time which elapsed in these experiments between the initiation of the trauma and the reduction of the pressure to the desired level varied approximately from one to six hours. The difference in weight of the traumatized and nontraumatized extremities in all instances amounted to more than 4 per cent of the body weight. Johnson and Blalock² found that when a normal dog is bled 0.5 per cent of its body weight at one hour intervals, the blood pressure is usually reduced to a very low level after from eight to ten hours. No evidence was found for the action of a histamine-like substance which causes an immediate general loss of fluid from the blood stream. However, these experiments were probably not of sufficient duration to take into account the effects of decomposition products which are slow in their action.

The present experiments were undertaken in order to attempt to determine whether or not slowly acting decomposition products are responsible for the decline in pressure after injury to large masses of

In order to coordinate the previous reports with our major problem, this general title has been adopted. The previous communications, (a) Mechanism and Treatment of Experimental Shock. I. Shock Following Hemorrhage, *Arch Surg* **15** 762 (Nov) 1927. (b) Trauma to Central Nervous System. Its Effect on the Cardiac Output and Blood Pressure. An Experimental Study, *ibid* **19** 725 (Oct) 1929, (c) Distribution of the Blood in Shock. The Oxygen Content of the Venous Blood from Different Localities in Shock Produced by Hemorrhage, by Histamine and by Trauma, *ibid* **20** 26 (Jan) 1930. (d) Experimental Shock. The Cause of the Low Blood Pressure Produced by Muscle Injury in Dogs, *ibid* **20** 959 (June) 1930, and (e) Trauma to the Intestines. The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure, *ibid* **22** 314 (Feb) 1931, are to be considered as papers I, II, III, IV and V of this series.

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1 Blalock, Alfred. Experimental Shock. The Cause of the Low Blood Pressure Produced by Muscle Injury in Dogs, *Arch Surg* **20** 959 (June) 1930.

2 Johnson, G. S., and Blalock, A. Unpublished Observations upon the Effects of the Loss of Whole Blood, of Blood Plasma and of Red Blood Cells.

muscle. The trauma was milder in degree, and the time that elapsed between the injury and the reduction of the pressure was longer than in the experiments that have been reported previously.

METHOD

Dogs were used in all experiments. Sodium barbital, 0.3 Gm per kilogram of body weight administered intravenously, was employed as the anesthetic. The anesthesia which was produced by this amount of barbital was sufficiently profound to permit of no evidence of pain when the trauma was instituted. An occasional animal gave evidence of the regaining of consciousness during the latter part of the long period of observation. In each instance, the original anesthesia was supplemented by morphine. The employment of sodium barbital in many other experiments, in the amount used in these experiments, has shown that it usually does not alter the blood pressure. However, in an occasional experiment, barbital alone causes a progressive decline in the blood pressure.

The level of the mean blood pressure was used as the criterion of the degree of shock. The pressure was determined by placing in the carotid artery a cannula which was connected to a mercury manometer. Infrequent observations on the pulse rate and the temperature were made.

In all experiments the injury was produced by striking one of the posterior extremities with a hammer. Most of the blows were struck over the thick flexor muscles of the thigh. The skin was not torn and no bones were broken. The length of time during which the leg was struck with the hammer was approximately ten minutes in most of the experiments. The trauma was always produced by the same person and the length of time that it would take a given amount of trauma to produce a decline in pressure could be estimated with fair accuracy in most instances.

After the blood pressure had reached the level which was desired, the differences in weight of the posterior extremities were determined. The level at which the amputations were performed was in the midabdominal region. After making a midline abdominal incision extending from the xiphoid process to the symphysis pubis, the aorta and vena cava were divided between ligatures. The symphysis pubis was divided with a saw and the bladder and the rectum were removed. The iliac vessels on each side were occluded. The upper and lower parts of the body were then severed by making transverse incisions in the midabdominal region at the same levels on both sides. Transverse division of the spinal column with a saw completed the amputation. In some experiments the lower part of the body was then divided into two equal halves by sawing longitudinally through the spinal column. The tail of the animal was then removed. In other experiments, division was effected by sawing just lateral to the vertebral column on each side. There was little loss of blood during these procedures.

This method of high amputation was chosen because it was found that trauma to an extremity produces an extravasation of blood not only into the local area but also into the loose tissues of the groin and flank. Amputation across the upper part of the thighs, the method used by Cannon and Bawls³ does not take into account this fluid which has been lost at a higher level.

³ Cannon and Bawls. Note on Muscle Injury in Relation to Shock. Report of Shock Committee. Medical Research Committee, no. 26, 1919, p. 19.

In most instances, a sample of blood was obtained for a hemoglobin determination at the beginning of the experiment and also just before its termination. After the posterior extremities had been removed, an attempt was made to collect all of the fluid from them. Each of the extremities was placed in a large basin. Multiple incisions were made through each, and every part was washed thoroughly with physiologic solution of sodium chloride. The percentage of hemoglobin in the fluid in the two basins was then determined. These figures, when divided by the percentage of hemoglobin of the blood and multiplied by the amount of fluid in the basins, gave the amount of blood that was recovered from the two parts. Obviously, it is impossible by this method to collect all of the blood.

In additional experiments, the effects of injecting all of the fluid that could be obtained from traumatized and nontraumatized extremities into other dogs were studied. In both types of experiments, the amputation was performed in the midabdominal region. The rectum, the genito-urinary organs and the spinal column were removed. In the experiments on nontraumatized parts, both extremities were used since the amount of fluid that could be recovered was small as compared with that from extremities that had been traumatized. After the extremities had been placed in basins, multiple incisions were made into each, and all of the fluid that was obtainable was washed out with salt solution. The tissues were squeezed vigorously in the attempt to secure all of the fluid. In the experiments on traumatized extremities the injury was graded so that the time that elapsed between the initiation of the trauma and the reduction of the pressure to the desired level varied from three hours to three days. After the traumatized extremity had been removed, the fluid was obtained from it as in the case of the nontraumatized extremities. In both types of experiments, the fluid which was kept at body temperature was introduced into the external jugular vein of another dog anesthetized by barbital. The blood pressure of the recipient was recorded during the introduction of the fluid. The fluid was given rapidly in all experiments except one, the total time consumed in most experiments being approximately five minutes. The total amount of fluid obtained from the extremities plus the salt solution used in recovering it equalled in most experiments approximately 400 cc. In one experiment the fluid was injected into the muscles of the posterior extremities of a normal dog, and in another it was introduced into the peritoneal cavity.

RESULTS

The effects of mild leg trauma on the blood pressure and the difference in weight of the two extremities were determined in fifteen experiments. In five of these the blood pressure was higher than 70 mm of mercury at the time of the amputation. These experiments are grouped together. In the remaining ten experiments, the blood pressure was lower than 70 mm of mercury.

1 *Experiments in Which the Blood Pressure Was Higher Than 70 mm of Mercury at the Time of the Amputation*—The average length of time between the traumatization and the amputation of the extremities was forty-four hours and thirteen minutes. The average mean blood pressure just prior to the amputation in the five experiments was 108 mm of mercury. The traumatized extremity was

definitely larger than the opposite normal one in all experiments. The average difference in weight of the two extremities amounted to 2.41 per cent of the body weight, the variation in the different experiments being from 1.62 to 3 per cent of the body weight. The amount of whole blood that was recovered from the traumatized extremities varied from 50 to 133 cc. There was an increase in the hemoglobin content of the blood in all experiments.

The observations in these experiments are given in table 1.

2 *Experiments in Which the Mean Blood Pressure Was Less Than 70 mm. of Mercury at the Time of Amputation*—In five of these experiments, the animals were allowed to die and in the remaining

TABLE 1.—*Experiments in Which the Mean Blood Pressure Remained at a Level Higher Than 70 Mm. of Mercury After Mild Leg Trauma*

Experiment	Weight of Dog, Kg.	Hemoglobin per Cent (Control)	Hemoglobin per Cent Before Amputation	Mean Blood Pressure Mm. Hg, Control	Mean Blood Pressure Mm. Hg. Before Amputation	Time Interval Between Trauma and Amputation, Hr., Min.	Weight of Traumatized Leg, Gm.	Weight of Nontraumatized Leg, Gm.	Difference in Weight of Legs, Gm.	Per Cent of Body Weight	Blood from Traumatized Leg, Cc.	Blood from Nontraumatized Leg, Cc.
1	9.1	66	76	134	105	19 15	1,240	990	250	2.75	50	4
2	10.5	81	91	148	93	70 50	1,200	1,110	170	1.62	54	4
3	12.7	74	82	150	74	2	2,060	1,480	580	4.00	133	16
4	12.8	69	95	155	95	20	2,240	1,840	400	2.90	102	7
5	9.7	70	82	156	168	48	1,200	1,025	175	1.80		

five the mean blood pressure just prior to the amputation ranged from 64 to 69 mm. of mercury. The time interval elapsing between the traumatization and the termination of the experiment ranged from nineteen hours to forty-nine hours and forty-five minutes, the average duration being thirty-two hours and sixteen minutes. The average difference in weight of the two extremities in the ten experiments amounted to 3.66 per cent of the body weight, the individual figures for the different experiments varying from 2.48 to 5.53 per cent. In eight of the ten experiments the difference amounted to more than 3 per cent of the body weight. The quantity of whole blood recovered from the traumatized extremity varied from 40 to 154 cc. There was a concentration of the blood in all experiments in which hemoglobin determinations were performed.

The values for these experiments are given in table 2.



The posterior extremities of an animal that died thirty-nine hours after the right leg was traumatized. The difference in weight of the two extremities amounted to 4.81 per cent of the body weight. This is experiment 4 recorded in table 2.

TABLE 2—Experiments in Which the Mean Blood Pressure Was Reduced to Less Than 70 Mm. of Mercury by Mild Leg Trauma

Experiment	Weight of Dog, Kg.	Hemoglobin per Cent, Control	Hemoglobin per Cent, Before Amputation	Mean Blood Pressure, Mm. Hg, Control	Mean Blood Pressure, Mm. Hg, Before Amputation	Time Interval Between Trauma and Amputation, Hr., Min.	Weight of Traumatized Leg, Gm.	Weight of Nontraumatized Leg, Gm.	Difference in Weight of Legs, Gm.	Per Cent of Body Weight	Blood from Traumatized Leg, Cc.	Blood from Nontraumatized Leg, Cc.
1	11.5	83	107	162	64	49 45	1,840	1,505	335	2.91		
2	11.2			134	68	26	1,700	1,320	380	3.48		
3	14.5			130	69	30 30	1,960	1,500	460	3.17		
4	16.0	78	92	155	Dead	39	2,470	1,700	770	4.81	154	13
5	20.5	87		174	Dead	30	2,040	2,240	200	3.41		
6	11.7	66		125	Dead	42	1,630	1,400	230	2.45		
7	6.1	69	100	134	66	17 30	970	765	205	3.36	40	4
8	9.3	58	60	122	66	29	1,425	910	515	5.53	114	10
9	13.4	70		158	Dead	40	2,190	2,640	450	4.10		
10	8.5	71		161	Dead	19	1,280	995	285	3.35		

The accompanying illustration shows the posterior extremities of an animal thirty-nine hours after one of the extremities was traumatized

3 *The Effects of Introducing into Dogs the Fluid Obtained from the Nontraumatized Extremities of Other Dogs*—Five experiments of this type were performed. In most instances the dog that was traumatized was larger than the recipient of the fluid. In four of the five experiments there was a marked decline in the blood pressure either during or immediately after the introduction of the fluid. One of the dogs died five hours after the fluid was given. It is believed that the other four would have recovered had they been given the opportunity.

These five experiments are described briefly in the first part of table 3.

4 *The Effects of Introducing into Dogs the Fluid Obtained from the Traumatized Extremities of Other Dogs*—Eleven experiments of this type were performed. In eight of these the fluid was introduced rapidly into the external jugular vein; in one it was slowly given intravenously, in one it was injected into the muscles of the legs and in the remaining experiment it was introduced into the peritoneal cavity. The results in these experiments were extremely variable. The animal that received fluid into the muscles of the thigh died eight hours later while the one that had fluid and lacerated muscle introduced into the peritoneal cavity recovered. In the one experiment in which the fluid was slowly introduced intravenously, the animal died two and one-half hours after the beginning of the injection and before it had been completed. In three experiments in which the fluid was rapidly introduced intravenously there was an initial rise in the blood pressure while in the remaining five there was a marked decline. Seven of the eight animals died after the fluid was administered. The interval of time that elapsed between the introduction of the fluid and death varied from several minutes to twenty-four hours. In several instances, autopsy revealed blood-stained fluid in the peritoneal cavity, macroscopic hemorrhages in several organs and a thickened, grayish gallbladder. In three of four experiments in which an extremity of a very fat dog was traumatized, it was observed that the giving of the fluid from this extremity to another dog produced almost immediate death. The respirations stopped several minutes before the heart stopped beating. Short intervals of time separating the trauma to the extremity and the introduction of the fluid into another animal seemed to be associated with just as severe a reaction as did the longer intervals.

The results of these experiments are given in brief in table 3.

TABLE 3—*The Effects of Introducing into Dogs the Fluid Obtained from Traumatized and Nontraumatized Extremities*

Experiment	Nature of Experiment	Time Interval Between Trauma and Amputation	Initial Effect of Injection on Blood Pressure	More Remote Effect of Injection on Blood Pressure	Comment
1	Normal extremities	No trauma	Fell from 130 to 58 mm immediately after injection ended	Returned to normal control level four hours later	Animal recovered
2	Normal extremities	No trauma	Fell from 113 to 57 mm during injection	Returned to normal control level three hours later	Later injection of equal amount of normal salt solution produced no alteration in blood pressure
3	Normal extremities	No trauma	Fell from 116 to 46 mm during injection	Rose slightly one hour later, animal died 5 hours after injection	Autopsy showed bloody fluid in peritoneal cavity, edema of gallbladder, injection of duodenum, hemorrhages of liver and spleen
4	Normal extremities	No trauma	Slight rise in blood pressure during injection	Blood pressure remained at normal level	
5	Normal extremities	No trauma	Fell from 150 to 50 mm during injection, returned to normal immediately	Practically normal 24 hours later	
6	Leg trauma	4 hours, 45 minutes	Rose from 100 to 145 mm	Slow decline, death six hours later	Bloody fluid in peritoneal cavity, hemorrhages in various organs
7	Leg trauma	3 hours	Slow introduction of fluid, first rise, later fall	Slow decline, death 2½ hours after injection started	Bloody fluid in peritoneal cavity, hemorrhages in various organs
8	Leg trauma	17 hours, 30 minutes	Fell from 134 to 64 mm and then rose to 150	Two hours later was 84, 4 hours later was 150	Animal killed 24 hours later, no free fluid, no gross hemorrhages, gallbladder normal, donor very fat
9	Leg trauma	70 hours	Fell from 120 to 77 mm during injection, immediate rise to 130	Five hours later was 66, died 22 hours after injection	Temp 92.8 F° before death, small amount of free fluid in peritoneal and pleural cavities, gallbladder thick walled
10	Leg trauma	29 hours	Rose from 127 to 136 during injection	Slow decline, died 5 hours later	Blood stained fluid in peritoneal cavity
11	Leg trauma	70 hours, 50 minutes	Immediate fall from 128 to 47 mm	Died 8 minutes after injection was started	Donor very fat dog, breathing ceased several minutes before heart stopped, beating, gallbladder presented normal appearance at autopsy
12	Leg trauma	20 hours	Immediate fall from 155 to 50 mm	Died 7 minutes after injection was started	Donor very fat dog, gallbladder thick walled and whitish, no free peritoneal fluid, respiratory death
13	Leg trauma	3 hours	Immediate fall from 118 to 20 mm	Died 10 minutes after injection was started	Donor very fat dog, respiratory death
14	Leg trauma	26 hours	Rose slightly during injection	Slow decline, died 7 hours after introduction of fluid	No autopsy
15	Leg trauma	5 hours	No alteration in pressure	Died 8 hours later	Fluid was injected into thigh muscle, none intravenously
16	Leg trauma	5 hours	Not determined	Animal recovered	Fluid and lacerated muscle introduced into the peritoneal cavity

COMMENT

In the previous experiments¹ on trauma to large masses of muscle, the time that elapsed between the initiation of the trauma and the reduction of the pressure to a low level varied from one to six hours. Although the experiments of Cannon and Bayliss² are not described in detail approximately the same interval of time elapsed. They found that there was not sufficient bleeding into the injured area to account by itself for the reduction in the blood pressure. Section of the upper lumbar cord in some of their experiments showed that the fall in blood pressure was not due to any general effect of the trauma on the circulation brought about by nervous agencies. It was believed that the continued fall in pressure following trauma was produced by the absorption of some depressant substance. In my experiments on severe trauma of short duration, the difference in the weight of the extremities in all instances amounted to more than 4 per cent of that of the total weight of the animal. Since bleeding a dog 4 per cent of its body weight during a similar period of time causes a marked decline in the blood pressure, the loss of blood into the injured area was believed to be responsible for the drop in the pressure. It was pointed out that the discrepancy between these results and those obtained by Cannon and Bayliss was probably due to the difference in the methods by which the posterior extremities were amputated. However, probably neither of these groups of experiments was of sufficient duration to rule out the effects of metabolites which are very slow in their actions. The time which elapsed between the traumatization and the amputation of the extremity in the present experiments varied from nineteen to seventy hours. Experiments of such long duration have the disadvantage that the animals have to be deeply anesthetized during the entire period and this probably alters somewhat their ability to tolerate such procedures as loss of blood. Deprivation of water and food alone for several days results in concentration of the blood³ and probably in a decrease in the ability to withstand hemorrhage. The giving of barbital does not alter appreciably the immediate tolerance to hemorrhage. The effect of barbital on the ability of the animal to withstand hemorrhage twenty-four or more hours after its administration has not been accurately determined, but it was definitely decreased in the several experiments which were performed. Dale⁴ found that a cat that had been anesthetized by ether for two hours would tolerate only

4 Underhill, F. P., and Kapsinow, R. The Influence of Water Introduction upon Blood Concentration Induced by Water Deprivation, *J. Biol. Chem.* **54**, 459, 1922.

5 Dale, H. H. Supplementary Note on Histamine Shock, Report of Shock Committee, Medical Research Committee, no. 26, 1919, p. 15.

one-fifth as much histamine without dying as would the same cat without an anesthetic. Similar studies have not been performed with histamine and barbital.

In the five experiments in which the blood pressure was higher than 70 mm of mercury at the time of the amputation, the average difference in the weight of the two extremities was 2.41 per cent of the body weight. The blood pressure at the termination of four of these experiments was higher than 90 mm of mercury. There was an easily apparent difference in the size of the extremities in all experiments. It is believed but not proved that the size of the traumatized extremity was smaller in some of these extremities at the time of the amputation than it was thirty-six hours after the receipt of the injury.

In the ten experiments in which the pressure was reduced to less than 70 mm of mercury the average difference in the weight of the two extremities was 3.66 per cent of the body weight. In the experiments in which it was determined, the whole blood that was recovered accounted for only about one fourth of this difference. Obviously it was impossible, by the method used, to recover all of the blood. However, it can be stated with certainty that the red blood cells constituted a relatively small part of the fluid which escaped into the injured area. The proportion was much smaller than in the previously reported experiments in which the trauma was more severe. The greater part of the fluid which was lost was probably blood plasma. There was concentration of the blood in all experiments in which determinations of the hemoglobin were performed. These tests were performed on blood from the femoral vein of the nontraumatized extremity. They indicate the minimum loss of blood through filtration of the plasma as any local retention of red cells would decrease the percentage. Observations of previous investigators indicate that the fluid that was lost into the traumatized area was mainly the plasma of the blood. Starling⁶ demonstrated that the walls of the blood vessels are normally impermeable to colloids. Scott⁷ showed that there is no protein in the fluid absorbed from the tissue spaces by the blood, although the fluid in these spaces contains protein. Dale and Laidlaw⁸ found that shock that is produced by histamine is not accompanied by an increase of the plasma proteins, and they expressed their belief that whole plasma rather than water escaped into the tissues through the altered capillaries.

6 Starling, E. H. On the Absorption of Fluids from the Connective Tissue Spaces, *J. Physiol.* **19** 312, 1896.

7 Scott, F. H. The Mechanism of Fluid Absorption from Tissue Spaces *J. Physiol.* **50** 157, 1915-1916.

8 Dale and Laidlaw. Histamine Shock, *J. Physiol.* **52** 355, 1918.

Gasser, Erlanger and Meek⁹ produced shock by clamping the aorta, and effected filtration of the whole plasma. Underhill¹⁰ and his associates stated that when fluid leaves the tissues and blood in response to local inflammatory reactions the fluid poured on the surface is plasma or at least modified plasma. In regard to pulmonary edema they stated, "Certain it is that in war gas poisoning in the production of pulmonary edema the fluid entering the lungs has almost the same composition as the blood plasma." The character of the fluid that escapes into tissues of the extremity that has been traumatized will be the study of a future investigation but it seems almost certain that its composition is practically that of whole blood plasma.

If it be granted for the moment that the fluid that is lost into the traumatized extremity has approximately the same composition as has whole blood plasma, the question then arises as to whether or not the loss of this amount of plasma could account for the reduction in the blood pressure that was found. Information in this respect is not definite. Kallius¹¹ stated that the serum and not the red blood cells is the important element in the replacement after an acute loss of blood. Abel, Rowntree and Turner¹² found that it was possible to withdraw by repeated bleedings in a single day a volume of blood more than twice that contained in the body, with no apparent injury to the animal if only the corpuscles suspended in Locke's solution were returned after each bleeding. However, in the present experiments there was no replacement of the fluid which was lost. Almost certainly there is some passage of water from the tissues into the blood stream, but probably a considerable portion of this is lost in the urine and the expired air. Morawitz¹³ found that he could keep animals alive after replacing two thirds of serum proteins by gum. Saline solution would not serve the purpose. Bayliss¹⁴ produced concentration by removing a part of the blood, defibrinating and centrifuging it and reinjecting the corpuscular

9 Gasser, Erlanger and Meek. Studies in Secondary Traumatic Shock. IV. The Blood Volume Changes and the Effect of Gum Acacia on Their Development, *Am J Physiol* **50** 31, 1919

10 Underhill, F. P., Carrington, G. L., Kapsinow, R., and Pack, G. T. Blood Concentration Changes in Extensive Superficial Burns and Their Significance for Systemic Treatment, *Arch Int Med* **32** 31 (July) 1923

11 Kallius, H. W. Experimentell Untersuchungen über die Wirkung des Serums bei der vitalen Bluttransfusion, *Deutsche Ztschr f Chir* **212** 289, 1928

12 Abel, Rowntree and Turner. Plasma Removal with Return of Corpuscles (Plasmapheresis), *J Pharmacol & Exper Therap* **5** 625, 1913-1914

13 Morawitz. Beitr z Chem Phys u Path **7** 153, 1906

14 Bayliss, W. M. The Action of Gum Acacia on the Circulation, *J Pharmacol & Exper Therap* **15** 29, 1920

layer The result of the experiment in which the largest proportion of plasma was removed is as follows

When 47 per cent of the plasma had been removed, the blood pressure had fallen to 75 mm of mercury from its original value of 163 mm The animal died at the following removal of blood equal to about 20 per cent of its original blood volume The method is therefore impracticable, but it makes evident the importance of the mere volume of the blood, since practically all the corpuscles were returned Similar experiments in which the whole of the defibrinated blood was returned to circulation had no such fatal effects

Gasser, Erlanger and Meek⁹ determined the blood volume in a large series of dogs and found the average to be 97 per cent of the body weight They estimated that the plasma constitutes 60 per cent of the volume of the blood The average difference in weight of the two extremities in the present experiments in which the blood pressure was reduced to less than 70 mm of mercury was 3.66 per cent of the body weight If all the fluid that was lost was whole plasma, this would mean that only 37 per cent of the original plasma was left in the blood stream This figure is definitely too low, as a moderate amount of the loss consisted of red blood cells However, the loss was sufficient to cause a marked elevation in the viscosity of the blood, which resulted in a great increase in the internal friction of the red cells against the vessel walls as has been demonstrated by Trevan¹⁵ The walls of the capillaries in the traumatized area allow the escape of proteins Concerning this condition, Bayliss¹⁴ stated

Since it is the osmotic pressure of the proteins that preserves the blood from a rapid filtering away of its liquid portion into the tissue spaces and causes re-absorption of fluid from them, while this osmotic pressure can only be effective as long as the concentration of proteins is unequal on the two sides of the membrane, it will be clear that if the proteins can diffuse through the membrane of the capillary wall, their concentration will become equal on both sides and there is no longer any force resisting filtration or causing re-absorption

Since the difference in the weight of the two extremities in most of the present experiments represented such a large volume of fluid which was almost certainly largely whole plasma, it is believed that the increased permeability of the capillaries is limited mainly, if not solely, to the traumatized area and that the decline in blood pressure results from the decrease in blood volume due to the loss into the injured part

The experiments in which the fluid was taken from a traumatized extremity and injected into another dog were undertaken with the idea that the effects of trauma of long duration might be different from those of short duration It was thought that this might throw some light on the rôle played by the decomposition products in the production

15 Trevan *Biochem J* 12 60, 1918

of the low blood pressure. The experiments were unsatisfactory for this purpose since it was found that the material that was obtained from normal extremities usually caused a decline in the blood pressure. In the experiments on traumatized extremities, the time interval elapsing between the trauma and removal varied from three to seventy hours, and no difference in the effects on introduction into other dogs was determined. Death resulted in most of the experiments. In three experiments in which the injured extremity was removed from a very fat dog, immediate death resulted in the recipient on the introduction of the fluid. The significance of this is not known.

SUMMARY

In experiments on dogs anesthetized by barbital the effects of mild trauma to one of the extremities were studied. The time interval that elapsed between the initiation of the trauma and the amputation of the extremities varied from seventeen to seventy hours. In five experiments the average of the mean blood pressures was 108 mm. of mercury at the time of the amputation, and the average difference in weight of the two extremities amounted to 2.41 per cent of the body weight. In ten experiments the mean blood pressure was less than 70 mm. of mercury at the time of the amputation and the difference in weight of the two extremities was 3.66 per cent of the body weight. Previous experimental work indicates that the fluid that was lost was mainly the whole plasma of the blood. Reasons are given for the belief that the loss of fluids into the traumatized region was the chief if not the sole cause for the reduction in the blood pressure.

In additional experiments the effects of injecting fluid obtained from extremities which had been traumatized into other dogs were studied. No conclusions could be drawn from these experiments, since the introduction of fluid obtained from nontraumatized extremities into other dogs finally caused a decline in the blood pressure.

EXPERIMENTAL SHOCK

x VII THE IMPORTANCE OF THE LOCAL LOSS OF FLUID IN THE PRODUCTION OF THE LOW BLOOD PRESSURE AFTER BURNS *

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The literature on the subject of burns is voluminous and the theories that have been offered as an explanation for the effects produced by burns are numerous. In 1898 the four prevailing theories as to the cause of death after extensive burns when Bardeen¹ reviewed the literature and presented his excellent studies were

1 It is due to interference with the respiratory, the excretory and the heat regulating functions of the skin. 2 It is due to vasomotor exhaustion. 3 It is caused by injury to the red blood cells with resulting thrombosis. 4 It is due to toxemia. Advances in the understanding of the mechanism whereby extensive burns produce death have not been marked during the past thirty years. The prevailing theory is and was that the deleterious effects are due to the absorption of toxic products from the injured area. On the contrary, distinct advances have been made in the treatment for burns in recent years, and the mortality rate has been lowered considerably. This is due in part to the fact that the importance of keeping the wounds from becoming infected has been appreciated. The use of agencies which supposedly prevent the absorption of toxins, such as epinephrine (Douglas²) and tannic acid (Davidson³), has given encouraging results. Robertson⁴ attributed the good results which he obtained by using the exsanguination-transfusion method to the elimination of the toxins.

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From the Department of Surgery, Vanderbilt University

1 Bardeen, C R. A Review of the Pathology of Superficial Burns, with a Contribution to Our Knowledge of the Pathological Changes in the Organs in Cases of Rapidly Fatal Burns, Johns Hopkins Hosp Rep **7** 137, 1898

2 Douglas, B. Restriction of Rate of Flow and Interchange in Capillaries, J A M A **81** 1937 (Dec 8) 1923

3 Davidson, E C. Tannic Acid in the Treatment of Burns, Surg Gynec Obst **41** 202, 1925

4 Robertson, B. Blood Transfusion in Severe Burns in Infants and Young Children, Canad M A J **11** 744, 1921

Underhill and his associates⁵ believed that the ill effects following burns were due to marked concentration of the blood, and they obtained excellent results by simply forcing fluids.

In previous experiments⁶ the amount of fluid that was lost from the blood vessels in the injured area after trauma to an extremity and to the intestines was determined. The present experiments were undertaken in order to determine the amount of fluid that escapes from the blood vessels at the site of extensive burns.

METHOD

Dogs were used in all experiments. A sufficient amount of sodium barbital (0.3 Gm per kilogram of body weight administered intravenously) was given to keep the animal deeply anesthetized during the experiment. The blood pressure was determined by placing in the carotid artery a cannula which was connected to a mercury manometer. The level of the mean blood pressure was used as the criterion of the degree of shock. The hair was removed from the body and extremities of the animals by the use of either fine clippers or a razor. The longitudinal midlines on both the dorsal and ventral surfaces of the dogs were marked with ink. A sample of blood for a hemoglobin determination was obtained from the femoral vein. With the animals profoundly anesthetized, varying amounts of one half of the body surface were burned with soldering irons. No attempt was made to measure the surface area which was burned, but in the greater portion of the experiments it equalled approximately one third of the entire body surface. In several experiments the area was definitely less than that. The time during which the irons were applied intermittently varied approximately from ten to forty minutes. The blood pressure was determined at frequent intervals throughout the experiments. After a decline in blood pressure of varying degree had been obtained in the different experiments, the amount of fluid that had accumulated in the burned area was determined. This was accomplished by dividing the animal's body into two equal halves. Incisions into the skin both dorsally and ventrally were made along the lines that had been marked at the beginning of the experiment. This was necessary, because the skin became retracted toward the burned side. The recti abdominales muscles were separated in the midline by an incision extending from the xiphoid process to the symphysis pubis. A saw was employed in splitting the sternum in the midline in a longitudinal direction. The animal's neck was cut across in a transverse direction at the same levels on the two sides. A saw was used for cutting across the cervical spinal column. The head of the animal was discarded. The symphysis pubis was divided with a saw. All of the intra-abdominal and intraperitoneal organs,

5 Underhill, F. P., Carrington, G. L., Kapsinow, R. K., and Pack, G. T. Blood Concentration Changes in Extensive Superficial Burns and Their Significance for Systemic Treatment, *Arch. Int. Med.* **32**: 31 (July) 1923.

6 Blalock, A. Experimental Shock. The Cause of the Low Blood Pressure Produced by Muscle Injury in Dogs, *Arch. Surg.* **20**: 959 (June) 1930, Trauma of Intestines. The Importance of the Local Loss of Fluid in the Production of Low Blood Pressure, *ibid.* **22**: 314 (Feb.) 1931, Experimental Shock. VI. The Probable Cause for the Reduction in the Blood Pressure Following Mild Trauma to an Extremity, this issue, p. 598.

including the diaphragm, were removed en masse. Turning to the dorsal surface of the animal, the skin incision was extended through the muscles on each side immediately lateral to the spinous processes. Employing a saw and beginning in the lower cervical region on each side, the ribs were divided at their junctions with the spinal column and the sacro-iliac joints were cut across. This resulted in a complete removal of the spinal column and tail which were discarded. The two halves of the body were then weighed and the difference in weight was determined. In eight of the experiments a sample of blood was obtained for a hemoglobin determination just prior to the performance of the amputation.

RESULTS

The application of heat to the skin of a dog does not cause blisters. There is no weeping from the surface of the skin. The appearance

The Effects of Burns

Experiment	Weight of Dog, Kg	Time Interval Between Burn and Amputation Hr., Min	Hemoglobin per Cent, Control	Hemoglobin, per Cent, Before Amputation	Blood Pressure mm. Hg Control	Blood Pressure Before Amputation mm. Hg	Weight of Burned Side Gm	Weight of Non-burned Side, Gm	Difference in Weight of Sides Gm	Per Cent of Body Weight
1	10.34	17	85	117	118	Dead	1,945	1,630	315	3.05
2	11.5	15	75		117	Dead	3,590	3,260	330	2.87
3	12.2	21			110	Dead	3,820	3,350	470	3.85
4	10.1	11			122	50	3,170	2,850	320	3.17
5	11.4	10 30			125	50	3,455	3,130	325	2.85
6	12.7	17	77	130	143	Dead	4,245	3,890	355	2.80
7	13.29	14 30	65		125	Dead	4,085	3,850	235	1.77
8	14.7	12	63	109	98	30	4,760	3,880	880	5.98
9	13.2	26	62		123	36	3,870	3,490	380	2.92
10	11.25	24	60	86	120	28	3,470	3,100	370	3.29
11	9.9	16	76		155	Dead	2,920	2,700	220	2.22
12	7.4	6	50	78	160	66	2,180	1,800	380	5.14
13	10.1	6	78	109	150	80	3,410	3,180	230	2.28
14	15.2	10			150	Dead	4,860	4,160	700	4.61
15	12.5	6	76	94	150	66	3,970	3,590	380	3.04
16	9.4	24	70	98	143	82	1,650	1,420	230	2.34
17	18.6	11	68		165	Dead	2,820	2,220	600	3.23
18	6.6	15			130	Dead	2,050	1,740	310	4.70

produced is similar to that seen after the application of tannic acid to a burned area in the human being. The skin feels much like leather. After the elapse of varying periods of time following the burn, depending on its severity, the subcutaneous tissues feel thickened and edematous.

Eighteen experiments were performed. The interval of time that elapsed between the burning and the division of the animal varied in the different experiments from six to twenty-six hours, the average time in all experiments being fourteen hours and thirty-three minutes. In three instances the mean blood pressure was 80 mm. of mercury or

more at the termination of the experiment, in six it varied from 28 to 66 mm of mercury and the remaining nine animals were allowed to die. In all experiments, the average difference in weight of the two sides of the body expressed in percentage of the initial weight of the animals was 3.34. In fourteen of the eighteen experiments the difference amounted to more than 2.75 per cent of the body weight. The figures for all experiments are given in the accompanying table.

Incisions into the burned area revealed the cause for the increase in weight of that side. The subcutaneous tissues were markedly edematous. That all the fluid did not accumulate immediately after the area was burned was shown by making incisions at various times after the injury and noting the progressive formation.

In the eight experiments in which hemoglobin determinations were performed, the burns caused a marked concentration of the blood. If the percentage of hemoglobin at the beginning of the experiments is considered to be 100, the average percentage at the termination is found to be 148.

COMMENT

In previous communications⁶ the amount of fluid that was lost from the injured area after severe trauma to an extremity, after mild trauma to an extremity and after trauma to the intestines was reported. Red blood cells constituted a small part of the loss after mild trauma to an extremity and after trauma to the intestines, while after severe trauma to an extremity the fluid that escaped was largely whole blood. It was concluded that the escape of fluid from the blood stream in the traumatized area was the chief if not the sole factor responsible for the reduction in the blood pressure. The fluid that escapes from the blood vessels into the subcutaneous tissues of a burned area contains practically no red blood cells. From the work of previous investigators, it would be expected that this fluid would have practically the same composition as the plasma of the blood. Gasser, Erlanger and Meek⁷ found that the protein content of the blood plasma underwent no marked change during the process of the concentration of the blood after the aorta had been clamped, and they believed that the plasma was lost mainly as a whole. Underhill⁸ stated that the fluid that escapes into the lungs in the pulmonary edema produced by war gases has almost the same composition as the blood plasma. Beard and I⁸ in unpublished

⁷ Gasser, Erlanger and Meek. *Studies in Secondary Traumatic Shock. IV. The Blood Volume Changes and the Effect of Gum Acacia on Their Development*, *Am J Physiol* **50** 31, 1919.

⁸ Beard and Blalock, A. *Unpublished Determinations on the Composition of the Fluid Which Escapes from the Blood Vessels in Leg Trauma, Intestinal Trauma and Burns*, 1930.

observations found that the fluid that collects in the subcutaneous tissues after burns has almost as high a protein content as has the plasma of the blood

The average difference in weight of the two sides of the body in the present experiments amounted to 3.34 per cent of that of the body. The question arises as to whether or not the loss of this amount of plasma could account for the reduction in the blood pressure. Even if it could be definitely proved that the decline in pressure in the present experiments was due solely to the loss of plasma, it would not rule out the action of possible toxic products after burns of longer duration. It is difficult to interpret the results of experiments of very long duration in which profound anesthesia and deprivation of food and water are complicating factors. In the present experiments the longest interval of time elapsing between the application of heat and the termination of the experiment was twenty-six hours. The incomplete experiments of Johnson and myself,⁹ in which an amount of blood which equals 0.5 per cent of the body weight is removed at one hour intervals, show that it is usually necessary to remove at least 4 per cent before the mean blood pressure will remain below 70 mm. of mercury. As regards the removal of plasma and reinjection of the cells over a similar period of time, it is found that the blood pressure is usually reduced to a low level after plasma amounting to approximately 3.5 per cent of the body weight has been removed. Bayliss¹⁰ found that the removal of 47 per cent of the plasma in a cat caused a reduction in the blood pressure from 163 to 75 mm. of mercury. The animal died following the removal of blood equal to about 20 per cent of its original blood volume. Gasser, Erlanger and Meek⁷ determined the blood volume in a large series of dogs and found the average to be 9.7 per cent of the body weight, and they estimated that the plasma constitutes 60 per cent of the weight of the blood. On comparing the loss of plasma in the present experiments (approximately 3.34 per cent of the body weight) with the estimated total of the animal, it is found that approximately 57 per cent of the total plasma escaped from the circulating blood stream. It is apparent that the loss of such a large amount of plasma would cause a concentration of the blood and an increase in the friction between the red blood cells and the walls of the vessels. It is likely that some of the fluid that was lost from the blood stream was replaced by the passage of water from the tissues of the body. Since no fluids were administered during the experiment, probably

9 Johnson and Blalock, A. Unpublished Observations upon the Comparative Effects of the Loss of Whole Blood and of Plasma, 1930

10 Bayliss, W. M. The Action of Gum Acacia on the Circulation, *J. Pharmacol. & Exper. Therap.* **15** 29, 1920

a large proportion of this was lost in the urine and in the expired air. At any rate, the passage of water from the tissues to the blood stream would not result in a replacement of the protein of the plasma. In addition to the loss of fluids in the urine and the expired air, another source, probably of small importance, is the dehydration of the skin produced as a direct result of the local application of heat. All of these factors are neglected in the determinations of the loss of fluid from the blood stream.

Underhill,¹¹ from his studies on poisoning by war gases, concluded that concentration of the blood exceeding the normal by 25 per cent is attended by grave symptoms and that a level maintained at 40 per cent or more above the normal is usually followed by death. The average increase in the concentration of the blood in the present experiments was 48 per cent. Whether the concentration of the blood is due to the loss of fluid exclusively into the injured area or whether there is a general increase in capillary permeability with loss of fluid as a result of toxic products cannot be stated definitely from the present experiments. The experiments of Bayliss and of Johnson and myself indicate that it is due solely or almost to the loss of fluid into the burned area alone. Bardeen¹ found swelling and focal degenerations of the lymphatic tissues of the body after burns. Weiskotten¹² stated that the suprarenal glands were swollen and deep red. There is a great amount of other good evidence which indicates that a toxin which exerts a general effect is formed. However, it is impossible to escape the fact that the loss of such large amounts of whole plasma into the burned area must play an important part in causing a reduction in the blood pressure as a result of the diminution in the blood volume. Regardless of whether or not death is due solely to the loss of plasma, the present experiments indicate that the fluid loss probably is the initiating factor in the decline of blood pressure. After the blood volume is reduced and the blood is very concentrated, it is likely that toxins if present, even in small amounts, will exert deleterious effects since elimination by the kidneys is greatly reduced. In the human being, the factor of loss of fluid after burns may be even more important than in the dog, since there is frequently copious weeping from the injured skin in man, and this is not encountered in dogs. It is entirely possible that such agencies as tannic acid and epinephrine exert their beneficial effects by preventing loss of fluids rather than by stopping the absorption of toxins.

11 Underhill, F. P. *The Lethal War Gases. Physiology and Experimental Treatment*. New Haven, Conn., Yale University Press, 1920.

12 Weiskotten, H. G. *Histopathology of Superficial Burns*. J. A. M. A. 72: 259 (Jan. 25) 1919.

SUMMARY

The effects of burns on the escape of fluid into the tissue spaces of the injured area have been determined in eighteen dogs anesthetized deeply by barbital. Varying amounts of one half of the body surface were burned, and the difference in weight of the two halves of the body was determined. In all instances the burned side was heavier, the average difference in weight in all experiments being 3.34 per cent of the total weight of the dog. The important rôle that this probably exerts in the reduction of the blood pressure has been discussed.

EXPERIMENTAL SHOCK

VIII THE COMPOSITION OF THE FLUID THAT ESCAPES FROM THE * BLOOD STREAM AFTER MILD TRAUMA TO AN EXTREMITY, AFTER TRAUMA TO THE INTESTINES AND AFTER BURNS *

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In previous communications¹ the amount of fluid that is lost from the blood stream at the site of injury after severe trauma to an extremity, after mild trauma to an extremity, after trauma to the intestines and after burns was reported. When an extremity is traumatized severely, the fluid that escapes into the injured subcutaneous tissues and muscles consists largely of whole blood. Some red blood cells escape from the blood vessels after mild trauma to an extremity and after trauma to the intestines, but the proportion is much smaller than after severe trauma. Burns are associated with the escape of clear fluid with few red cells into the subcutaneous tissues. Gasser, Erlanger and Meek² found that the protein content of the plasma of the blood underwent no marked change during the process of the concentration of the blood after clamping the aorta, and they believed that the loss was for the most part whole plasma. Underhill³ stated that the fluid that escapes in the pulmonary edema produced by war gases has nearly the same composition as the blood plasma.

It would be expected that the loss of whole plasma would be followed by more deleterious effects than would result from the loss of diluted plasma or of water. The present experiments were undertaken

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* From the Department of Surgery of the Vanderbilt University

1 Blalock, Alfred. Experimental Shock. The Cause of the Low Blood Pressure Produced by Muscle Injury, *Arch Surg* **20** 759 (June) 1930, Trauma to the Intestines. The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure, *ibid* **22** 314 (Feb) 1931, Experimental Shock VI. The Probable Cause for the Reduction in the Blood Pressure Following Mild Trauma to an Extremity, this issue, p 598, Experimental Shock VII. The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure After Burns, this issue, p 610.

2 Gasser, Erlanger and Meek. Studies in Secondary Traumatic Shock. IV. The Blood Volume Changes and the Effect of Gum Acacia on Their Development, *Am J Physiol* **50** 31, 1919.

3 Underhill, F P. The Lethal War Gases, Physiology and Experimental Treatment, New Haven, Conn. Yale University Press 1920.

in order to determine the composition of the fluid that escapes into or from the injured area because of several different procedures

METHODS

Dogs were used in all experiments. The animals were deeply anesthetized by sodium barbital (0.3 Gm per kilogram of body weight given intravenously). The level of the mean blood pressure was used as the criterion of the degree of shock. This was determined by placing in the carotid artery a cannula which was connected to a mercury manometer. In some instances, samples of blood were obtained from the femoral vein at the beginning and termination of the experiments, and the hemoglobin was determined with a Sahli hemoglobinometer.

Samples of blood and of fluid were collected at the same time if possible. In some experiments the blood and fluid were oxalated while in others the analyses were performed on the serum. The results were approximately the same whether plasma or serum was used.

The analyses of fluid and plasma or serum were carried out as follows. The sugar was determined by the method of Benedict.⁴ The sodium sulphate, which was kept as the concentrated solution, was added with the other reagents at the time of the determination. The nonprotein nitrogen was determined by the method of Folin and Wu.⁵ The chlorides were determined by the method of Whitehorn.⁶ The Gunning⁷ modification of the Kjeldahl method was used in determining the total nitrogen. One cubic centimeter of plasma or serum was the amount used in all experiments. The mixture was heated for more than three hours. The time of distillation was forty-five minutes. One-tenth normal sulphuric acid was used for the absorption of the ammonia, and the excess was titrated with one-tenth normal sodium hydroxide. The figures corresponding to the total nitrogen were multiplied by the factor 6.25 for obtaining the figures for total protein which are used in the tables.

RESULTS

1 *Mild Trauma to an Extremity*—Four experiments were performed in which one of the extremities was struck repeated blows with a hammer. The skin was not torn, and no bones were broken. In three of the four experiments, samples of blood were obtained for the various analyses before the trauma was instituted. The time interval which elapsed between the initiation of the trauma and the reduction of the blood pressure to the desired level varied from twenty-two to thirty-one hours. The mean blood pressure at the time of the termination of the experiment in two instances was above 90 mm of mercury and in two instances was below 50 mm. The trauma was followed by a definite concentration of the blood in all experiments. After the blood pressure had reached the desired level, approximately 15 cc of blood was removed from the femoral vein. An incision was then made

⁴ Benedict, S. R. The Estimation of Sugar in Blood and Normal Urine. *J. Biol. Chem.* **68**: 759, 1926.

⁵ Folin and Wu. A System of Blood Analysis, *J. Biol. Chem.* **38**: 81, 1919.

⁶ Whitehorn, J. C. A System of Blood Analysis, *J. Biol. Chem.* **45**: 449, 1920.

⁷ Gunning, J. W. *Ztschr. f. anal. Chem.* **28**: 188, 1889.

into the traumatized area and enough of the subcutaneous tissues to yield about 10 cc of fluid was removed and centrifugated

The chloride content of the blood plasma was approximately the same at the beginning and the end of the experiments. The fluid recovered from the traumatized area had approximately the same chloride content as the plasma of the blood. The sugar content of the blood plasma was lower at the end than at the beginning of the experiments. The sugar content of the blood plasma was higher than that of the fluid in all experiments. The abnormally high values for sugar content

TABLE 1—*The Composition of the Fluid Obtained from the Subcutaneous Tissues After Mild Trauma to an Extremity*

Experiment	Time Between Trauma and Amputation, Hr	Time Sample Was Obtained	Control Blood Pressure, Mm Hg	Blood Pressure Before Amputation, Mm Hg	Control Hemoglobin, per Cent	Hemoglobin Before Amputation, per Cent	Chlorides in Blood Plasma, Mg per 100 Cc	Chlorides in Fluid of Leg, Mg per 100 Cc	Sugar in Blood Plasma, Mg per 100 Cc	Sugar in Fluid of Leg, Mg per 100 Cc	Nonprotein Nitrogen in Blood Plasma, Mg per 100 Cc	Nonprotein Nitrogen in Fluid of Leg, Mg per 100 Cc	Total Protein in Blood Plasma, per Cent	Total Protein in Fluid of Leg, per Cent
1	30	Just before amputation	156	95	69	95	630 Serum	627	100 Serum	64	90 Serum	80	5.0	6.3
2	25	Control, before trauma	140		103		660		123		33		6.4	
		Just before amputation		42		115	622	636	76	75	63	66	7.1	8.0
3	31	Control, before trauma	143		68		607		166		34.2			
		Just before amputation		92		89	650	686	137	117	48	60	9.9	9.2
4	22	Control, before trauma	170		88		660		186		31		6.7	
		Just before amputation		48		112	673	613	133	80	108	100	7.7	10.6

are probably due to the barbitol anesthesia. The nonprotein nitrogen content was definitely higher at the end than at the beginning of the experiment. The values for the fluid from the traumatized extremity were approximately the same as those for the blood plasma. In the two experiments in which it was determined, the total protein of the plasma was greater at the termination than at the beginning of the experiments. In three of the four experiments, the total protein content of the fluid from the traumatized extremity was higher than that of the plasma.

The results of these four experiments of mild trauma to an extremity are given in table 1.

2 *Trauma to the Intestines*—Five experiments were performed. Before the traumatization was begun, the blood pressure and the hemoglobin were determined and a sample of blood was obtained from the femoral vein for the various analyses. The trauma was produced by pinching the intestines between the fingers. The intestines were not delivered from the peritoneal cavity and the fluid that escaped from the traumatized areas accumulated in the peritoneal cavity. The intestines were pinched continuously in most of the experiments, and the time that elapsed between the initiation of the trauma and the reduction of the pressure to a level less than 70 mm of mercury was approximately six hours. At intervals throughout the course of the experiments, the blood pressure was determined, a sample of blood was obtained from the femoral vein and fluid was collected from the peritoneal cavity. This

TABLE 2—*The Composition of the Fluid that Escapes Through the Peritoneum of the Intestines During Traumatization*

Time	Me in Blood Pressure, Mm Hg	Hemoglobin in Blood, per Cent	Chlorides in Blood Plasma, Mg per 100 Cc	Chlorides in Fluid, Mg per 100 Cc	Sugar in Blood Plasma, Mg per 100 Cc	Sugar in Fluid, Mg per 100 Cc	Nonprotein Nitrogen in Blood Plasma, Mg per 100 Cc	Nonprotein Nitrogen in Fluid, Mg per 100 Cc	Total Protein in Blood Plasma, per Cent	Total Protein in Fluid per Cent
9 30 a m, control	160	71	587		121		33		5.4	
11 35 a m	82		610	656	166	181	39	41	6.3	4.9
1 35 p m	103		620	643	133	163	42	46	6.7	4.9
2 50 p m	90		617	633	135	138	48	50	6.7	4.9
3 50 p m	58	106	620	636	133	115	57	60	5.6	5.0

type of experiment presented advantages over the other types studied because the fluid could be obtained from the peritoneal cavity as frequently as desired without making an incision into the injured area. At the termination of the experiment a sample of blood was obtained from the femoral vein for a hemoglobin determination. There was a marked concentration of the blood in all experiments.

There was very little alteration in the chlorides of the blood plasma throughout the course of the experiments. The chloride content of the fluid obtained from the peritoneal cavity was approximately the same as that of the blood plasma obtained at the same time. There were marked alterations in the sugar content of both the plasma and the fluid from the peritoneal cavity throughout the experiments, but the values for both in most instances were approximately the same. The values for nonprotein nitrogen were nearly identical for the samples of plasma and fluid obtained at the same time. There was a progressive rise in the nonprotein nitrogen content of both the plasma and the fluid

throughout the experiments. The total protein of the plasma usually increased slightly during the traumatization but returned to the previous control level after a marked decline in blood pressure had occurred. The total protein content of the plasma was usually slightly greater than that of the fluid.

TABLE 3—*The Composition of the Fluid that Escapes Through the Peritoneum of the Intestines During Traumatization*

Time	Mm Hg	Hemoglobin in Blood, per Cent	Chlorides in Blood Plasma, Mg per 100 Cc	Chlorides in Fluid, Mg per 100 Cc	Sugar in Blood Plasma, Mg per 100 Cc	Sugar in Fluid, Mg per 100 Cc	Nonprotein Nitrogen in Blood Plasma, Mg per 100 Cc	Nonprotein Nitrogen in Fluid, Mg per 100 Cc	Total Protein in Blood Plasma, per Cent	Total Protein in Fluid, per Cent
9 25 a m, control	175	76	597		151		42		67	
10 50 a m				602		363		37		73
11 50 a m	106		580	557	333	350	37	36	65	64
12 50 a m	130		580	569	231	245	37	34	73	58
3 50 p m	116		567	590	216	258	40	42	98	70
5 50 p m	54	125	577	552	449	449	58	63	69	68

TABLE 4—*The Composition of the Fluid that Escapes Through the Peritoneum of the Intestines During Traumatization*

Time	Mm Hg	Hemoglobin in Blood, per Cent	Chlorides in Blood Serum, Mg per 100 Cc	Chlorides in Fluid, Mg per 100 Cc	Sugar in Blood Serum, Mg per 100 Cc	Sugar in Fluid, Mg per 100 Cc	Nonprotein Nitrogen in Blood Serum, Mg per 100 Cc	Nonprotein Nitrogen in Fluid, Mg per 100 Cc	Total Protein in Blood Serum, per Cent	Total Protein in Fluid, per Cent
10 00 a m, control	130	84	603		111		30		67	
11 15 a m	120			613		150		31		61
12 15 a m	120			619		121		33		54
1 15 p m			660	644	90	114	37	33	60	51
2 15 p m	125			638		117		35		50
3 15 p m				627		108		44		55
4 15 p m	108			607		89		48		56
5 15 p m	59	112	569	660	60	109	66	60	67	67

Three of the five experiments are given in tables 2, 3 and 4. The remaining two presented similar results. In two of the three experiments given in the tables the whole fluid and blood were analyzed, while in the remaining experiment the serum alone was used for the analyses.

It is possible that some concentration of the fluid that escaped into the peritoneal cavity resulted from evaporation or absorption. In view of the fact that the fluid was collected frequently, it is believed that this factor is negligible.

3 *Burns*—Six experiments were performed. The hair was removed by the use of fine clippers or a razor. With the animal deeply anesthetized, a sample of blood was obtained for the control determinations. Approximately one third of the body surface was then burned with soldering irons. The time interval that elapsed between the application of the irons and the reduction of the pressure to the desired level varied

TABLE 5—*The Composition of the Fluid that Escapes Into the Subcutaneous Tissues After Burns*

Experiment	Time Between Burn and Amputation, Hr	Control Blood Pressure, Mm Hg	Blood Pressure Before Amputation, Mm Hg	Time Sample Was Obtained	Chlorides in Plasma, Mg per 100 Cc	Chlorides in Fluid, Mg per 100 Cc	Sugar in Blood Plasma, Mg per 100 Cc	Sugar in Fluid, Mg per 100 Cc	Nonprotein Nitrogen in Blood Plasma, Mg per 100 Cc	Nonprotein Nitrogen in Fluid, Mg per 100 Cc	Total Protein in Blood Plasma, per Cent	Total Protein in Fluid per Cent
1	24	142	80	Control, before burning	620 Serum		150 Serum		25 Serum		8.9 Serum	
				Just before amputation	627 Serum	686	163 Serum	134	70 Serum	62	8.4 Serum	7.6
2	11	170	Dead	Control, before burning	617 Serum		88 Serum		33 Serum		5.2 Serum	
				Fluid after death		633		40		48		6.1
3	14	128		Control, before burning	587		132		39		8.3	
				Two hours after burning	600		130		39		8.2	
			Dead	After death		613		78		90		7.0
4	15	118		Control, before burning	594		142		80		9.3	
				Two hours after burning	594		148		35		9.3	
			Dead	After death	613	627	66	102	126	92	10.2	8.2
5	20	175		Control, before burning	660		160		30		6.8	
			86	Just before amputation	666	712	125	133	79	79	7.9	5.9
6	17	175		Control, before burning	621		181		35		6.9	
			57	Just before amputation	643	683	117	133	75	79	8.0	

from eleven to twenty-four hours in the different experiments. After the blood pressure had reached this level a sample of blood was obtained from the femoral vein. An incision was then made into the inguinal region of the burned side, and a large block of the edematous tissue was removed. Enough fluid for all the analyses was obtained by centrifuging this tissue.

The chloride content of the fluid that was obtained from the subcutaneous tissues was slightly higher in all experiments than was that of the blood plasma. In most experiments the difference in the sugar

content of the fluid and the plasma was not marked. The nonprotein nitrogen content of the plasma was elevated after the burn was produced. In most experiments, values for the nonprotein nitrogen of the fluid and the blood plasma were approximately the same. The total proteins of the blood plasma usually increased slightly following the burns. The total protein content of the blood plasma was usually about 20 per cent higher than that of the subcutaneous fluid.

The results of these experiments are given in table 5.

COMMENT

The relationship between the chloride content of the plasma of the blood and of the fluid that escaped from the blood vessels is such as would be expected from known osmotic laws. The values for the sugar content of the plasma and that of the fluid varied greatly in the different experiments. Cannon⁸ found a normal or slightly increased amount of blood sugar in wound shock, while Fabre, Wertheimer and Clogne⁹ reported a reduced content of blood sugar. Duval and Grigaut,¹⁰ and Aub and Wu¹¹ reported an increase in the nonprotein nitrogen of the blood plasma in traumatic shock. Their observations agree with those found in these experiments. It was also found that the nonprotein nitrogen content of the fluid that escapes from the injured vessels is approximately the same as that of the blood plasma. The increase in the nonprotein nitrogen of the plasma is probably due either to tissue destruction or to the decrease in urinary secretion which accompanies the low blood pressure. It is believed that none of these analyses is of major importance in the present study.

As regards the loss of fluid into the injured area in the experiments which have been reported previously,¹ the analyses of particular interest in the present experiments are those of the protein content of the plasma and of the fluid that escaped from the blood vessels at the sites of injury. In most of the experiments the protein content of the fluid that was obtained from the damaged area was nearly identical with that of the blood plasma. The fluids contained in the tissue spaces normally have the same composition in salts as the blood plasma. There is a free interchange of water, salts and substances with a small molecular weight

8 Cannon, W. B. Acidosis in Cases of Shock, Hemorrhage and Gas Infection, *J. A. M. A.* **70** 531 (Feb. 23) 1918.

9 Fabre, Wertheimer and Clogne. Quelques considerations sur les modifications humorales et les reactions de l'organisme dans le shock, *Bull. et mem. Soc. de chir. de Paris* **45** 8, 1919.

10 Duval and Grigaut. L'intoxication par les plaies de guerre. La retention azotee des blesse, *Compt. rend. Soc. de biol.* **81** 873, 1918.

11 Aub and Wu. Studies in Experimental Traumatic Shock. III. Chemical Changes in the Blood, *Am. J. Physiol.* **54** 416, 1920.

between the blood stream and the tissue spaces. This is not true of colloids (mainly proteins), as the blood vessels are normally impermeable to them. This is important because the suction force (osmotic pressure) exerted by the plasma proteins normally serves to counterbalance almost exactly the filtration force due to the hydrostatic pressure in the capillaries. This fact was demonstrated by the experiments of Starling¹² and more recently by those of Schade¹³ and his co-workers. Schade stated that the edema fluid that occurs in cardiac failure or nephrosis has a very low protein content. A high protein content of edema fluid can be due only to increased capillary permeability and indicates that the trauma must have resulted in severe capillary damage.

In regard to the mechanisms that operate after hemorrhage and after trauma, Cannon¹⁴ stated

In normal individuals after hemorrhage, there soon occurs a dilution of the blood due to the passage of fluid from the tissue spaces into the blood stream. The mechanism of this occurrence is explained by Starling as due to such reduction of the blood pressure in the capillaries that the filtration pressure from within them no longer offsets the greater osmotic pressure of the plasma as compared with the lymph, and consequently water passes into the blood stream. It is one of the unexplained features of shock that with the low venous and arterial pressures this process does not occur. Instead, the plasma as a whole makes its escape through the vessel walls.

Studies by Harris and Blalock¹⁵ show very little loss of fluid from the tissues after hemorrhage and only a small fall in the hemoglobin content of the blood. After hemorrhage, the diminished filtration pressure without an increase in the osmotic pressure of the tissue proteins would be expected to cause the passage of some water into the blood stream. This accounts for the small decrease in hemoglobin usually observed. In the types of shock studied in this paper, it seems that the fluid once escaped cannot be reabsorbed to any marked degree because the osmotic pressure in the injured tissue spaces is practically equivalent to that of the blood. The diminution in the capillary pressure probably tends to draw fluid into the blood stream in the noninjured areas. However, if this results, the increase in the mechanical pressure which it causes would tend to cause further loss of fluid into the injured tissues. It is believed that the results of these experiments indicate that the loss of

12 Starling, E. H. On the Absorption of Fluids from the Connective Tissue Spaces, *J. Physiol.* **19** 312, 1896.

13 Schade, H. IX. Ueber Quellungsphysiologie und Oedementstehung. *Ergebn. d. inn. Med. u. Kinderh.* **32** 425, 1929.

14 Cannon, W. B. *Traumatic Shock*, New York and London, D. Appleton & Company, 1923, p. 44.

15 Harris and Blalock. Unpublished Observations on the Water Content of the Tissues after Hemorrhage and after Trauma, 1930.

plasma proteins is the most important factor in the production of the low blood pressure after the procedures reported here

SUMMARY

Studies have been made of the plasma of the blood and of the fluid that escaped from the blood stream at the site of the injury after mild trauma to an extremity, after trauma to the intestines and after burns. The analyses included determinations of the content of chlorides, sugar, nonprotein nitrogen and total protein. The fluid that escaped from the blood vessels of the injured area had approximately the same composition in all of these constituents as the plasma of the blood. Reasons are given for believing that the loss of plasma proteins at the site of injury is the most important factor in the production of shock caused by the experimental methods used in this study.

EXPERIMENTAL SHOCK

IN A STUDY OF THE EFFECTS OF THE LOSS OF WHOLE BLOOD, OF
BLOOD PLASMA AND OF RED BLOOD CELLS *

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In previous experiments,¹ the amount of fluid that was lost from the blood vessels in traumatized areas has been determined. The fluid that escapes from the blood vessels into an extremity as a result of severe trauma consists largely of whole blood. The composition of the fluid that escapes from or into the injured area as a result of mild trauma to an extremity, trauma to the intestines and burns of the body surface was found by Beard and one of us (A B)² to be nearly identical with that of the blood plasma. These experiments were all performed on dogs anesthetized by barbital. It was believed that the loss of fluid from the blood vessels in the injured area was the chief if not the sole factor in the production of the low blood pressure.

The present experiments were undertaken in order to determine the tolerance of anesthetized dogs to the loss of whole blood or plasma, not into or from the injured area as in the previous experiments, but from a cannula placed in an artery. It seemed that this would give information as to whether or not the reduction in pressure in the previous experiments was due exclusively to the loss of fluid at the site of the trauma. An effort was made to remove the blood or plasma at the same rate as it was probably lost in the earlier experiments. In addition to affording a comparison with the experiments in which trauma was instituted, the present experiments were undertaken in order to determine the specific

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1 Blalock, Alfred. Experimental Shock. The Cause of the Low Blood Pressure Produced by Muscle Injury, Arch Surg 20 759 (June) 1930, Trauma to the Intestines. The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure, ibid 22 314 (Feb) 1931, Experimental Shock VI The Probable Cause for the Reduction in the Blood Pressure Following Mild Trauma to an Extremity, this issue, p 598, Experimental Shock VII The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure After Burns, this issue, p 610

2 Beard, J W, and Blalock, A. Experimental Shock VIII The Composition of the Fluid That Escapes from the Blood Stream After Mild Trauma to an Extremity, After Trauma to the Intestines, and After Burns, Arch Surg, this issue, p 617

effects of the removal of whole blood, of blood plasma and of red blood cells

METHODS

Dogs were used in all the experiments. Sodium barbital, 0.3 Gm per kilogram of body weight administered intravenously, was employed as the anesthetic. The same anesthetic in identical amounts had been used in the previous experiments in which injury was inflicted. In some of the longer experiments, the barbital was supplemented by morphine sulphate in order to keep the animals quiet. The blood pressure was determined by placing in the carotid artery a cannula which was connected to a mercury manometer. The blood was removed through a cannula in the femoral artery. The hemoglobin was determined at the beginning and end of the experiments by the use of a Sahli hemoglobinometer.

Three types of experiments were performed. In the first group, an amount of whole blood corresponding to 0.5 per cent of the body weight was removed at one hour intervals in some experiments and at six hour intervals in others. In the second group of experiments, an amount of whole blood which equaled 1 per cent of the body weight was removed at one hour or six hour intervals. The blood was defibrinated and centrifugated. The red blood cells plus enough plasma to equal one half of the sample that had been withdrawn were introduced into the external jugular vein. The temperature of the blood at the time of its introduction was approximately that of the body. The interval which elapsed between the removal of the blood and the reintroduction was approximately twenty-five minutes. In the third group of experiments, an amount of whole blood which equaled 1.25 per cent of the body weight was removed at one hour or six hour intervals. The blood was defibrinated and centrifugated. The blood plasma was pipetted off and an amount of plasma equal to 60 per cent of the blood that had been removed was introduced into the external jugular vein. It was necessary to remove more blood in these experiments than in those of the second group because the red blood cells constitute only about 40 per cent of the whole blood. The bleedings were continued in all experiments until death resulted.

In three control experiments, the effects of reintroducing into the circulation blood which had been defibrinated and centrifugated were studied. An amount of whole blood corresponding to 1 per cent of the body weight was removed at one hour intervals until ten bleedings had been performed. The blood was defibrinated and centrifugated and all of it was introduced into the external jugular vein. The blood pressure was approximately the same at the conclusion of these experiments as it was at the beginning, indicating that the defibrinated blood did not produce deleterious effects.

The experimental procedures that were employed in the second and third groups are not exactly comparable to those of the first group because a larger amount of whole blood was temporarily removed, and because the blood was defibrinated and centrifugated before part of it was reintroduced into the circulation. These objections were partially met by performing the experiments that were mentioned in the last paragraph and by experiments similar to those which will be reported for the first group except that whole blood amounting to 1 per cent of the body weight was removed at one hour and six hour intervals, it was defibrinated and centrifugated exactly as in groups 2 and 3, and whole blood equal to one half of the volume which had been removed was reintroduced into the circulation. The results were practically identical with those obtained in group 1, and indicate that the different observations in the three groups of experiments are not due to variations in the experimental methods. The results of these experiments are given in table 1. In some of the experiments in groups 2 and 3, the bleedings

TABLE 1—The Effects of Removing at One Hour Intervals and at Six hour Intervals Whole Blood Amounting to 1 Per Cent of the Body Weight, Defibrinating It, Centrifuging It and Reintroducing One Half of the Amount Removed

Time Between Bleedings	Experiment	Weight of Dog, Kg	Hemoglobin, per Cent, Control	Amount Bled Each Time, Gm	First Bleeding		Second Bleeding		Third Bleeding		Fourth Bleeding		Fifth Bleeding		Sixth Bleeding		Seventh Bleeding		Eighth Bleeding		Ninth Bleeding		Tenth Bleeding		Hemoglobin, per Cent at Termination	Total per Cent Bled
					B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P		
One hour intervals	1	17.0	79	170, re placed 85	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	79	45
					B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P		
					B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P		
Six hour intervals	2	19.1	95	191, re placed 95.5	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	96	50
					B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P		
					B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P		
Six hour intervals	3	16.1	108	161, re placed 80.5	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	99	50
					B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P		
					B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P		
Six hour intervals	1	12.5	70	125, re placed 62.5	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	81	45
					B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P		
					B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P		
Six hour intervals	2	12.5	76	125, re placed 62.5	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	87	30
					B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P		
					B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P		

* B P, blood pressure

were performed twice as frequently and only one-half as much blood was removed each time. The results were approximately the same as in the experiments in which the procedures were not altered.

RESULTS

Group 1 Removal of Whole Blood Amounting to 0.5 Per Cent of the Body Weight—A, Six Experiments in Which the Bleedings Were Performed at One Hour Intervals. The total amount of blood removed in the different experiments ranged from 3.5 to 6.5 per cent of the body weight. The average of the experiments was 5.1 per cent. The average length of time that elapsed between the first bleeding and death was nine hours and forty-five minutes. In most of the experiments the hemoglobin showed a decline of approximately 14 per cent of that of the control determinations.

The results of these experiments are given in table 2.

B, Six Experiments in Which the Bleedings Were Performed at Six Hour Intervals. The total amount of blood removed in the different experiments ranged from 2 to 4 per cent of the body weight. The average loss was 2.92 per cent of the body weight. The average length of time that elapsed between the first bleeding and death was thirty-one hours and thirty minutes. The hemoglobin was usually decreased by about 9 per cent.

The results of these experiments are given in table 3.

Group 2 Removal of Blood Plasma Amounting to 0.5 Per Cent of the Body Weight—A, Eight Experiments in Which the Bleedings Were Performed at One Hour Intervals. The total amount of fluid removed in percentages of body weight in the different experiments varied from 2.5 per cent plasma and 1 per cent whole blood to 3.5 per cent plasma and 0.85 per cent whole blood. The sum of these figures is 4.05 per cent, which was the average total loss of plasma and whole blood. The figure for the whole blood is necessarily included because the animals died before the red blood cells from the last bleeding had been replaced. The average length of time that elapsed between the first bleeding and death was six hours and thirty-four minutes. The average increase in the hemoglobin was 34 per cent of the control figures.

The results of these experiments are given in table 4.

B, Five Experiments in Which the Bleedings Were Performed at Six Hour Intervals. The total amount of fluid removed in percentages of body weight in the different experiments varied from 2 to 3.5 per cent plasma. The average loss was 2.4 per cent plasma and 0.2 per cent whole blood. The sum of these figures is 2.6 per cent, which was the average total loss of plasma and whole blood. The figure for the whole blood is included because two animals died before the red blood cells

TABLE 2—The Effects of Removing Whole Blood Amounting to 0.5 Per Cent of the Body Weight and at One Hour Intervals, No Replacement

Experiment	Weight of Dog, Kg	Hemoglobin, per Cent, Control		First Bleeding		Second Bleeding		Third Bleeding		Fourth Bleeding		Fifth Bleeding		Sixth Bleeding		Seventh Bleeding		Eighth Bleeding		Ninth Bleeding		Tenth Bleeding		Eleventh Bleeding		Twelfth Bleeding		Thirteenth Bleeding		Hemoglobin, per Cent at Termination	Total per Cent Bled
		Amount Bled Each Time, Cc	B P * Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After			
1	13.1	75	65	136	121	136	115	140	124	146	128	137	119	120	72	117	73	94	73	86	60	82	Died								50
2	14.25		72	122	108	125	116	137	130	144	135	140	130	131	130	134	129	116	105	96	67	70	12	Died							50
3	11.0	75	70	160	138	157	147	148	131	115	130	140	120	120	116	111	74	86	51	85	36									67	
4	11.6	87	58	152	150	158	150	136	140	146	126	150	125	123	108	124	110	113	111	111	105	102	60	72	17	50	30				75
5	11.0	78	57	115	100	117	100	113	90	92	58	79	51	56	36	29	19	Died													65
6	10.2	85	96	118	118	150	150	151	153	158	150	154	145	150	138	131	126	121	112	118	100	96	92	96	88	87	60	61	37	78	65
																															Died

* B P, blood pressure

TABLE 3—The Effects of Removing Whole Blood Amounting to 0.5 Per Cent of the Body Weight and at Six Hour Intervals, No Replacement

Experiment	Weight of Dog, Kg	Hemoglobin, per Cent, Control		First Bleeding		Second Bleeding		Third Bleeding		Fourth Bleeding		Fifth Bleeding		Sixth Bleeding		Seventh Bleeding		Eighth Bleeding		Hemoglobin, per Cent at Termination	Total per Cent Bled
		Amount, Gm	Time, Ce	B P * Before	B P After	B P * Before	B P After	B P * Before	B P After	B P * Before	B P After	B P * Before	B P After	B P * Before	B P After	B P * Before	B P After	B P * Before	B P After		
1	13.0	87	65	176	118	111	114	136	112	56	39	Died									20
2	13.6	87	68	140	125	110	130	138	132	124	115	120	106	84							25
3	8.2	70	11	124	121	126	124	120	120	118	110	106	89	84							35
4	8.0	53	10	126	118	117	107	110	108	107	87	112	90	65							30
5	8.1	81	12	139	129	130	130	120	118	114	115	120	118	118							40
6	11.75	81	60	158	158	158	140	106	105	88	84	12	29	Died							25

* B P, blood pressure

TABLE 4—The Effects of Removing Blood Plasma Amounting to 0.5 Per Cent of the Body Weight at One Hour Intervals

Experiment	Weight of Dog, Kg.	Hemoglobin, per Cent, Control	Amount Bled Each Time, Cc	First Bleeding	Second Bleeding	Third Bleeding	Fourth Bleeding	Fifth Bleeding	Sixth Bleeding	Seventh Bleeding	Eighth Bleeding	Hemoglobin, per Cent at Termination	Total per Cent Bled
				B P + Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After		
1	9.5	63	100 replaced 40	115	122	75	116	107	136	92	116	58	2.5 plus 1% whole blood
2	8.4	71	84 replaced 42	161	160	134	132	110	126	88	64	Died	2.5 plus 1% whole blood
3*	13.4		77 replacement	120	110	134	105	130	120	112	78	106	3.55 plus 0.83% whole blood
4	12.9	71	129, replaced 61	115	145	130	120	135	110	119	108	70	3.5 plus 1% whole blood
5	12.5	80	125, replaced 63	123	102	115	88	115	84	123	100	87	3.5 plus 1% whole blood
6*	17.2		113, replacement	178	132	166	150	165	170	146	147	12	3.20 plus 1% whole blood
7	9.3		77, replaced 31	114	108	110	90	116	80	100	70	35	3.5 plus 1% whole blood
8*	9.55	70	48, replaced 24	154	138	136	110	140	98	140	92	100	3.25

* In experiments 3 and 6, the amount removed at each bleeding was approximately, but not exactly, 0.5 per cent of the body weight. In experiment 8, bleedings were performed twice as frequently, and only one half as much blood was removed each time.

TABLE 5—The Effects of the Removal of Blood Plasma Amounting to 0.5 Per Cent of the Body Weight at Six Hour Intervals, Cells Replaced

Experiment	Weight of Dog, Kg.	Hemoglobin, per Cent, Control	Amount Bled Each Time, Cc	First Bleeding		Second Bleeding		Third Bleeding		Fourth Bleeding		Fifth Bleeding		Sixth Bleeding		Seventh Bleeding		Hemoglobin, per Cent at Termination	Total per Cent Removed
				B P + Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After		
1	10.0	79	100, replaced 50	138	94	120	66	96	58	76	73	Died						86	2.0
2	5.7	68	87, replaced 11.5	124	108	130	115	115	40	72	32	Died						86	2.0
3	9.4	81	94, replaced 47	148	125	148	129	170	88	95	85	60	44	Died				106	2.0 plus 0.5% whole blood
4	11.6	81	116, replaced 58	140	140	148	120	135	108	120	64	112	80	102	60	100	07 Died	97	3.5
5*	11.2	66	132, replaced 66	146	120	120	85	108	47	92	67	90	55	45	Died			81	2.5 plus 0.5% whole blood

* In experiment 5, bleedings were performed twice as frequently and only half as much blood was removed each time.

from the last bleeding had been replaced. The average length of time that elapsed between the first bleeding and death was twenty-eight hours and twenty-four minutes. The average alteration in the hemoglobin was an increase of 24 per cent over the normal.

The results of these experiments are given in table 5.

In two additional experiments whole blood amounting to 0.83 per cent of the body weight was removed at six hour intervals, and after centrifugation the red cells were replaced in enough saline solution to equal the volume of the blood that had been removed. The plasma was estimated as constituting 60 per cent of the whole blood. In one experiment the loss that produced death was 3.5 per cent plasma and 0.83 per cent whole blood, and in the other experiment 3 per cent plasma and 0.83 per cent whole blood. The total loss that was tolerated was definitely greater than that in the experiments in which the plasma was not replaced by salt solution.

Group 3 Removal of Red Blood Cells Amounting to 0.5 Per Cent of the Body Weight—A, Six Experiments in Which the Bleedings Were Performed at One Hour Intervals. The total amount of fluid removed in the different experiments in percentages of the body weight varied from 2.5 per cent of red blood cells to 4.0 per cent of red blood cells and 0.63 per cent of whole blood. The average loss was 3.67 per cent red blood cells and 0.52 per cent whole blood. The sum of these figures is 4.19 per cent, which was the average total loss of red blood cells and whole blood. The average length of time that elapsed between the first bleeding and death was seven hours and seventeen minutes. The average alteration in the hemoglobin was a decline of 49 per cent of that of the control determinations.

The results of these experiments are given in table 6.

B Four Experiments in Which the Bleedings Were Performed at Six Hour Intervals. The loss of fluids in the different experiments varied from 2.5 per cent red blood cells to 2.5 per cent red blood cells and 1.23 per cent whole blood. The average loss in the different experiments was 2.6 per cent red cells and 0.62 per cent whole blood. The average total loss of red cells and whole blood in percentages of body weight was 3.22. The average length of time that elapsed between the first bleeding and death was thirty hours and fifty-three minutes. There was an average decrease in hemoglobin of 30 per cent of the control determinations.

The results of these experiments are given in table 7.

COMMENT

These experiments afford a comparison with those performed earlier,¹ in which the amount of fluid lost from the blood stream in injured

Table 6—The Effects of Removing Red Blood Cells Amounting to 0.5 Per Cent of the Body Weight at One Hour Intervals

Experiment	Weight of Dog, kg.	Hemoglobin, per Cent, Control	Amount Bled Each Time, cc	First Bleeding		Second Bleeding		Third Bleeding		Fourth Bleeding		Fifth Bleeding		Sixth Bleeding		Seventh Bleeding		Eighth Bleeding		Ninth Bleeding		Hemoglobin, per Cent at Termination	Total per Cent Bled
				B P + Before	B P + After	B P Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After		
1	9.5	72	117, replaced 71.5	153	148	136	116	151	140	138	140	160	131	116	93	151	77	118	55	Died	35	3.5 plus 1.25% whole blood	
2	10.0	48	137, replaced 83	117	108	113	92	122	108	110	106	115	105	116	85	106	60	88	50	36	Died	25	1.0 plus 0.63% whole blood
3	9.9	82	125, replaced 75	124	90	130	111	131	131	135	128	117	80	136	80	121	71	110	57	39	Died	38	1.0 plus 0.63% whole blood
4*	12.6	72	138, replaced 95	116	118	110	92	140	113	115	106	148	90	113	106	130	67	100	38	32	Died	26	1.0 plus 0.63% whole blood
5	11.5	75	115, replaced 87	175	108	110	66	125	85	106	48	96	37	Died								18	2.5
6*	9.5	70	60, replaced 36	118	110	116	111	118	120	130	126	138	118	130	10	111	73	105	Died		11	1.0	

* In experiments 4 and 6, bleedings were performed twice as frequently, and only one half as much blood was removed each time
† B P, blood pressure

Table 7—The Effects of the Removal of Red Blood Cells Amounting to 0.5 Per Cent of the Body Weight at Six Hour Intervals

Experiment	Weight of Dog, kg.	Hemoglobin, per Cent, Control	Amount Bled Each Time, Cc	1st Bleeding		Second Bleeding		Third Bleeding		Fourth Bleeding		Fifth Bleeding		Sixth Bleeding		Hemoglobin, per Cent at Termination	Total per Cent Removed
				B P * Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After	B P Before	B P After		
1	10.55	72	1.0, replaced 78	126	116	125	130	126	120	120	85	110	18	100	Died	54	2.5 plus 1.25% whole blood
2	13.85	85	172, replaced 103	160	140	145	101	108	72	98	68	96	61	90	Died	68	2.5 plus 1.27% whole blood
3	15.75	85	196, replaced 117	130	116	170	150	140	108	115	68	97	61	70	Died	48	3.0
4	15.55	78	161, replaced 96	155	158	158	110	156	99	132	63	67	10	Died		25	

* B P, blood pressure

areas had been determined. The experiments in which whole blood amounting to 0.5 per cent of the body weight was removed at one hour intervals correspond roughly to the experiments³ in which one of the posterior extremities was traumatized severely with a hammer. In the eight experiments reported previously in which one of the posterior extremities was traumatized severely, the average length of time that elapsed between the initiation of the trauma and the reduction of the blood pressure to an average mean of 58 mm of mercury was three hours and thirteen minutes. The difference in weight of the two extremities equaled 5.3 per cent of the body weight. In the present experiments in which whole blood amounting to 0.5 per cent of the body weight was removed at one hour intervals, the average length of time between the first bleeding and death was nine hours and forty-five minutes. The average loss of whole blood that produced death was 5.1 per cent of the body weight. In these experiments, there was a slight decline in the percentage of hemoglobin, while in the experiments on leg trauma there was a slight rise. This difference is probably due to the loss of a greater proportionate amount of plasma than of red blood cells in the experiments on leg trauma, while whole blood was lost in the present ones.

In twelve experiments on intestinal trauma reported previously⁴ the average length of time between the initiation of the trauma and the reduction of the blood pressure to an average mean of 48 mm of mercury was five hours. The calculated average loss of fluid from and into the traumatized area was 4.48 per cent of the body weight. The fluid that escaped from the traumatized intestine was found by Beard and one of us (A. B.)² to have almost the same composition as the plasma of the blood. In the present experiments in which plasma of the blood amounting to 0.5 per cent of the body weight was removed at one hour intervals, the average length of time between the first bleeding and death was six hours and thirty-four minutes. The average loss of fluid that produced death, expressed in percentages of body weight, was 3.2 per cent plasma and 0.85 per cent whole blood or a total of 4.05 per cent. The slightly larger loss of fluid that was tolerated after trauma to the intestines may be due to the fact that it was lost slowly and continuously while in the experiments employing bleeding, rather large amounts were withdrawn at one hour intervals. The average increase in the hemoglobin above the normal in the experiments on intestinal trauma was 38 per cent and in the experiments on removal of plasma it was 34 per cent.

3 Blalock (footnote 1, first reference)

4 Blalock (footnote 1, second reference)

In ten experiments reported previously in which one of the posterior extremities was only moderately traumatized, the average length of time that elapsed between the initiation of the trauma and the reduction of the blood pressure to an average mean of 33 mm of mercury was thirty-two hours and sixteen minutes. The average difference in the weight of the two posterior extremities amounted to 3.66 per cent of the body weight. The fluid that accumulated in the traumatized area contained relatively few red blood cells, and its composition was found by Beard and one of us (A. B.)² to be approximately the same as that of the blood plasma. In the present experiments in which blood plasma amounting to 0.5 per cent of the body weight was removed at six hour intervals, the average length of time between the initial bleeding and death was twenty-eight hours and twenty-four minutes. The average loss of fluid that produced death, expressed in percentages of body weight, was 2.4 per cent plasma and 0.2 per cent whole blood or a total of 2.6 per cent. The average increase in the hemoglobin above the normal in the four experiments on leg trauma in which it was determined was 27 per cent. In the experiments in which plasma was removed at six hour intervals, the average increase was 24 per cent.

In eighteen experiments reported previously in which part of the body surface was burned, the average length of time that elapsed between the injury and the reduction of the blood pressure to an average mean of 28 mm of mercury was fourteen hours and thirty-three minutes. The average difference in the weights of the burned and non-burned halves of the body amounted to 3.34 per cent of the body weight. This difference consisted largely of fluid that accumulated in the subcutaneous tissues at the site of the burns. The composition of this fluid was found by Beard and one of us (A. B.)² to be approximately the same as that of the blood plasma. There were few red blood cells in it. The duration of the experiments on the effects of burns was intermediate between those in which plasma was removed at one hour and at six hour intervals. As has been stated previously, the total loss of fluid in the experiments in which plasma was removed at one hour intervals was 4.05 per cent of the body weight, and when it was removed at six hour intervals the loss was 2.6 per cent of the body weight. The difference in weight of the two sides of the body (3.34 per cent of the body) is approximately the mean of these two figures. The hemoglobin showed an average increase of 48 per cent above the normal in the nine experiments in which it was determined after burns.

It is interesting to note that the animals that had one extremity moderately traumatized tolerated a slightly greater loss of fluid than the animals that were burned. The duration of the experiments was longer in the instances of trauma of the leg. It may be due to the fact that some red blood cells as well as plasma were lost as a result of traumatiz-

ing an extremity, while burning the part apparently caused a loss of plasma alone. The present experiments show that the loss of whole blood is tolerated better than is the loss of plasma alone. It may be that toxins were partially responsible for the reduction in the blood pressure after the burns. This does not seem likely in these experiments of short duration in which the tolerance to loss of plasma was practically the same after the burns and after the removal of plasma from the femoral artery.

It was found in these and in the previous experiments that an occasional animal dies after only a very small amount of fluid has been lost. It was probably due to the barbitol, which is apparently toxic to a small percentage of animals. For example, one animal died after red blood cells amounting to only 15 per cent of the body weight had been removed. Two animals died in less than forty-eight hours without the removal of any fluid from the blood stream. However, in the great majority of animals, the blood pressure is not affected markedly by the giving of barbitol in the amounts used in these experiments. In studying the effects of severe injury, deep narcosis is necessary, and barbitol seems more satisfactory than any other anesthetic that has been tried. As has been stated previously, it was used in the present experiments in order that the results might be compared with those in which trauma was instituted. Otherwise, it is believed that a lighter anesthesia would have been more satisfactory for studying the comparative effects of the loss of whole blood, of blood plasma and of red blood cells.

The results of these experiments show that under the existing circumstances, animals withstand the loss of a greater amount of fluid when the removals are at one hour intervals than at six hour intervals. As has been stated previously, the animals were anesthetized deeply and they were deprived of food and water. Harris and one of us (A. B.)⁵ found that not a great deal of water passes from the body tissues into the blood stream after hemorrhage or trauma under barbitol anesthesia. Probably the greater part of this is lost in the expired air, urine and feces.

In the present experiments, dogs usually withstood the loss of a greater amount of whole blood than they did of blood plasma alone or of red blood cells alone. The exception to this was in the experiments in which the removals were performed at six hour intervals when there was a slightly greater tolerance to the loss of red blood cells than of whole blood. The loss of red blood cells alone was tolerated slightly better than was the loss of blood plasma alone. It is believed that the results are comparable because in some experiments in which the effects of the

⁵ Harris, P. N., and Blalock, A. Unpublished Observations on the Water Content of the Tissues After Hemorrhage and After Trauma.

loss of whole blood were determined, the blood was defibrinated and centrifugated as in the experiments on the removal of plasma and red blood cells. In several experiments sodium citrate was used as an anticoagulant instead of defibrinating the blood and the results were approximately the same. In order to remove red blood cells or plasma amounting to 0.5 per cent of the body weight, it was necessary to withdraw temporarily a larger amount of blood than in the experiments on the removal of whole blood. This objection was partially overcome by performing the bleedings twice as often in some of the experiments and removing only one-half as much blood each time. It seems very definite that the loss of red blood cells is tolerated better than the loss of plasma for it was necessary to remove a larger amount of whole blood in order to be able to leave out of the circulation a given amount of red blood cells than is the case in studying the effects of the removal of plasma. This is true since the plasma constitutes about 60 per cent of the volume of the blood.

SUMMARY

The comparative effects of the removal of whole blood, of plasma and of red blood cells have been determined in thirty-five dogs anesthetized by barbitol. The results indicate that the loss of whole blood is usually tolerated better than is the loss in equal amounts of either blood plasma or red blood cells. The animals withstand the removal of a slightly larger volume of red blood cells than of blood plasma.

The results obtained in these experiments have been compared with those reported previously on the effects of severe trauma to an extremity, mild trauma to an extremity, intestinal trauma and burns. They indicate that the cause for the reduction in the blood pressure after the various types of injury was the loss of whole blood or of plasma from the blood stream at the site of the trauma. It does not seem necessary to assume the action of a poison which exerts a general bodily effect.

EXPERIMENTAL SHOCK

X OBSERVATIONS ON THE WATER CONTENT OF THE TISSUES OF THE BODY AFTER TRAUMA AND AFTER HEMORRHAGE

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In the normal person or animal, following hemorrhage there occurs a passage of some fluid from the tissue spaces into the blood stream, thereby resulting in a dilution of the blood. Starling¹ believed this to be due to such reduction of the filtration pressure in the capillaries that the osmotic pressure of the plasma proteins is no longer counterbalanced. Cannon² stated that it is one of the unexplained features of shock not due to hemorrhage that with the low venous and arterial pressure this process does not occur. Some information in this respect has been reported in previous papers of this series. The amount of whole blood or of plasma that was lost from the blood stream at the site of injury was determined after severe trauma to an extremity,³ after trauma to the intestines,⁴ after mild trauma to an extremity⁵ and after burns⁶. Comparison of the figures obtained in these experiments with those found by Johnson and one of us (A B)⁷ in determining the amount of loss of whole blood and of plasma that produces death in animals anesthetized by barbital indicates that the loss of fluid into the traumatized area was the chief, if not the sole, cause for the decline in the blood pressure. If it is true that the fluid that is lost from the blood stream at the site of

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From the Department of Surgery, Vanderbilt University

1 Starling, E H. On the Absorption of Fluids from the Connective Tissue Spaces, *J Physiol* **19** 312, 1896

2 Cannon, W B. *Traumatic Shock*, New York, D Appleton & Company, 1923

3 Blalock, Alfred. Experimental Shock. The Cause of the Low Blood Pressure Produced by Muscle Injury, *Arch Surg* **20** 759 (June) 1930

4 Blalock, Alfred. Trauma to the Intestines. The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure, *Arch Surg* **22** 314 (Feb) 1931

5 Blalock, Alfred. Experimental Shock. VI The Probable Cause for the Reduction in the Blood Pressure Following Mild Trauma to an Extremity, *Arch Surg*, this issue, p 598

6 Blalock, Alfred. Experimental Shock. VII The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure After Burns, *Arch Surg*, this issue, p 610

7 Johnson, G S, and Blalock, A. Experimental Shock. IX A Study of the Effects of the Loss of Whole Blood, of Blood Plasma and of Red Blood Cells. *Arch Surg*, this issue, p 626

the injury is sufficient to account for the reduction in the blood pressure, there is probably no general increase in capillary permeability with loss of fluid from all of the capillaries of the body. On the contrary, it seems likely that the capillaries in uninjured parts would probably function as do those of the body after hemorrhage in allowing water to pass into them in an effort to increase the volume of the blood. The studies of Beard and one of us (A. B.)⁸ show that the fluid that escapes from the blood stream at the site of injury after mild trauma to an extremity, after trauma to the intestines and after burns has approximately the same composition as the plasma of the blood. This observation is of particular importance as regards the content in proteins because the osmotic pressure exerted by the plasma proteins serves to counterbalance the filtration force due to the hydrostatic pressure in the capillaries. It seems likely that the fluid once escaped could not be reabsorbed to any marked degree because the osmotic pressure in the injured tissue spaces is practically equivalent to that of the blood. However, it seems probable that the decrease in capillary pressure resulting from the loss of plasma at the site of the injury would cause some fluid to pass into the blood stream in the uninjured parts of the body. If this results, the increase in capillary pressure that would be caused by the passage of water into the blood stream in uninjured areas would probably cause the further loss of fluid through the injured capillaries.

The present experiments were undertaken in order to determine the water content of the tissues of injured and uninjured parts of the body after trauma to the intestines, trauma to an extremity and burns. For purposes of comparison, the water content of the tissues after the removal of whole blood and of blood plasma from the femoral artery was also determined.

METHODS AND RESULTS

All of the experiments were performed on dogs. The total number of animals used was sixty-seven. They were anesthetized by sodium barbital, which was administered intravenously (0.3 Gm. per kilogram of body weight). The same anesthetic in identical amounts had been employed in the previous experiments on the effects of trauma and hemorrhage. In fact, many of the determinations reported in this paper were performed on tissues obtained from the animals in which other studies on the effects of loss of fluid were being carried out. The blood pressure was determined by placing in the carotid artery a cannula which was connected to a mercury manometer. A Sahli hemoglobinometer was employed in determining the hemoglobin.

Tissues varying in weight usually from 1 to 2 Gm. were placed in small beakers, the weight of which had been determined previously. By the use of a small pair of sharp scissors, the tissues were cut into many pieces. This was done in order to facilitate the drying. The weight of the beaker plus the tissue

⁸ S. Beard, J. W., and Blalock, A. Experimental Shock. VIII. The Composition of the Fluid That Escapes from the Blood Stream After Mild Trauma to an Extremity, After Trauma to the Intestines and After Burns. Arch. Surg. this issue, p. 617.

was determined. They were then placed for approximately 48 hours in an oven, the temperature of which was kept at as nearly 105 degrees centigrade as possible. At the end of this time, they were again weighed. From these figures, the content of the tissues in water or in solids was determined.

Two different types of experiments were performed.

Group 1—In the first group of experiments, the percentage in solids of the various tissues was determined in normal animals and in those in which a low blood pressure had been produced by mild trauma to an extremity, by trauma to the intestines and by burning part of the body surface. Analyses were performed on tissues from the liver, lung, kidney, intestine, heart muscle, brain, spleen and skeletal muscle. In the experiments on trauma to an extremity, skeletal muscle was obtained from the traumatized as well as the nontraumatized side. In the experiments on burns, in addition to the other tissues, samples were taken from the subcutaneous tissues of both the burned and nonburned areas and from the skeletal muscle of both the injured and noninjured parts. In all instances, the piece of skeletal muscle was removed from one of the flexor muscles of the thigh and the heart muscle was obtained from the left ventricle. The subcutaneous tissues were removed from the inguinal region. The specimens of brain tissue were taken from the cerebrum. They included both white and gray matter, the water content of which is different, and the results were probably of little value. Attempts were made to obtain blocks of brain tissue of the same thickness in each experiment.

The results that were obtained in all of these experiments are given in table 1.

It is to be seen that there is a good deal of variation in the individual figures for the experiments of the control group as well as the others. The most significant observation is that the average of the figures for the same organ is approximately the same for the control experiments as for those in which a low blood pressure had been produced by injury. Leaving out of consideration the determinations on the tissues that were traumatized, the greatest variation between the averages for the different tissues in the control group and those after the three varieties of injury is that the content in solids of the skeletal muscle was 2.3 per cent higher after mild trauma to an extremity than was the average figure for the control group. In no other instance was the average difference as much as 2 per cent. In practically all instances, the average figure for solids was slightly higher for the experiments in which the blood pressure was low than in the control experiments.

In the experiments on trauma to one extremity, the muscle of the injured side had a lower percentage of solids than muscle from the opposite normal extremity. On the contrary, muscle obtained from an extremity the skin of which had been burned had a higher percentage of solids usually than muscle from the opposite extremity. The sub-

cutaneous tissues of an area that had been burned had a content in water several times as great as that of subcutaneous tissue from other parts of the body. The traumatized intestine had a slightly lower average percentage of solids than was found for the intestines in the control experiments.

Obviously, comparisons are not entirely satisfactory in which the control determinations and the experiments proper are performed on

TABLE 1—*The Percentage in Solids of the Tissues After the Various Procedures*

Proce- dure	Ex- peri- ment	Per cent Mean age Blood in Pres- sure, in Hemo- globin	Percentage of Solids										Mus- cle of Trau- ma- tized Side	Sub- cuta- neous Tis- sue	Sub- cuta- neous Tis- sue of Burned Side	Dura- tion of Ex- peri- ment, Hr.
			Liv- er	Lung	Kid- ney	In- tes- tine	Heart	Brain	Spleen	Mus- cle	Mus- cle Side	Sub- cuta- neous Side				
Nor- mal con- trols	1		26.1	21.7	23.2	27.4	22.9	24.0	22.0	28.3						
	2			21.3	22.1	26.5	22.1	26.0	23.7	31.6						
	3		26.0	20.4	20.8	21.1	20.7	20.0	21.0	26.5						
	4		26.4	20.5	22.2	22.0	20.7	24.9	20.9	24.6						
	5		28.7	20.0	20.8	20.7	21.4	24.9	21.7	24.7						
	6		27.2	21.0	20.0	20.8	21.9	23.2	22.5	25.3						
	7		25.5	19.6	21.1	19.8	21.6	24.0	20.6	24.7						
	8		28.5	22.3	20.5	22.8	22.2	23.3	22.2	31.4						
	Averages		26.9	20.9	21.3	22.7	21.7	23.8	21.8	27.1						
Mild leg trau- ma	1	105	12	26.9	21.6	24.6	25.4	24.3	21.0	21.3	26.8	26.6				47
	2	58	26		23.4	22.4	24.4	24.5	22.9	22.4	31.4	23.9				50
	3	72	11	26.9	22.2	23.4	26.8	23.3	24.3	22.2	34.3	25.7				23
	4			24.1	19.2	19.1	22.6	22.6	23.3	21.6	20.2	20.3				38
	5			26.1	20.3	20.0	25.8	23.6		22.4	34.1	25.9				30
	6	60	45	26.6	20.6	20.0	23.8		22.4	21.5	25.2	18.7				18
	7	95	38	23.4	21.9	21.7	23.5	21.9	24.7	21.7	33.9	25.1				31
	8	41	12	26.5	22.8	24.6	24.3	23.7	25.4	22.8		27.0				25
	9	87	31	26.4	22.8	21.6	23.0	23.8	23.9	21.8		25.0				31
	10	49	27	26.4	23.5	24.1	24.8	22.4	23.7	25.1		30.3				22
	Averages			26.1	21.8	22.6	24.4	23.3	23.5	22.3	29.4	24.9				
Intes- tinal trau- ma	1	58		27.8	23.2	25.6	20.9	22.8	24.0		26.9					6
	2	10		27.0	24.5	21.4	23.1	23.8	26.6		28.2					7
	3		6	27.4	21.9	21.3	24.3	21.8	21.3	20.6	27.4					5
	4	53	33	27.7	22.0	20.8	20.5	22.9	28.9	22.8	27.4					7
	5	49	64	28.6	23.1	22.3	20.8	23.0	26.7	22.9	27.7					8
	6	56	49	26.8	21.8	22.3	20.0	22.6	22.8	21.1	27.2					6
	Averages			27.6	22.8	22.3	21.6	22.8	25.1	21.9	27.5					
Burns	1	78		27.0	23.4	22.1	24.4	22.1	23.4		25.5	29.8	85.3	30.0		11
	2	50		28.2	23.1	23.5	23.9	25.7	25.1		30.5	30.4	71.8	18.0		11
	3			26.2	21.3	22.1	23.4	23.2	20.8		23.8	25.0	72.3	16.1		17
	4			23.1	21.7	21.3	23.5		23.4		23.8	29.9	63.7	13.7		14
	5		38	26.5	22.7	22.1	21.7	22.5	21.7		24.3	24.6	46.6	10.7		16
	6	75	40	25.9	24.2	22.1	26.0	23.0	22.7		29.6	29.4	79.5	21.7		24
	7										25.7	26.8	75.2	22.3		22
	Averages			26.5	22.7	22.2	23.8	23.3	22.9	23.1	27.2	28.2	70.6	18.9		

different animals. If tissues are to be taken from parts of the body such as the heart and lungs it is necessary that different animals be used. Since the muscles and skin contain more than 50 per cent of the water of the body, experiments were performed in which samples of muscle skin and blood were obtained before and after the various procedures.

Group 2—In the second group of experiments, the percentage in solids or in water of the blood, skeletal muscle and skin was determined before and after the various procedures. Eight different types of experi-

ments were performed. The total number of experiments was thirty-six. The samples of blood were removed from the femoral veins. Muscle and skin were removed from symmetrical parts of the body at the beginning and end of the experiments. In the greater number of experiments, the samples of muscle were from the two pectorals. In some experiments, the specimens were removed from one of the flexor muscles of the two forearms.

In the first five experiments, the animals were anesthetized by barbital, and specimens were taken for analysis. After periods of time varying from twenty-six to forty-seven hours, the second samples were removed. No water or food was given and these experiments were used simply as controls for the other experiments in which procedures in addition to the giving of barbital were carried out. The blood pressure remained the same or fell slightly during the period of observation. The average increase in hemoglobin was 18 per cent of the control reading. The average content in solids of the blood rose from 18.1 to 20 per cent, of the muscle from 23.6 to 25.6 per cent and of the skin from 37.1 to 39.2 per cent.

In the next five experiments, whole blood amounting to 0.5 per cent of the body weight was removed from the femoral arteries of dogs at one hour intervals until death resulted. Specimens of blood, muscle and skin were obtained at the beginning of the experiments and after the blood pressure had fallen to a low level. The mean blood pressure at the time the second series of samples were obtained varied from 20 to 64 mm. of mercury. The average decrease in the hemoglobin was 14.6 per cent of the control figures. The average content in solids of the blood declined from 19.5 to 18.4 per cent. The content in solids of the muscle increased from 24.7 to 25.2 per cent, and that of the skin from 41.5 to 44.4. The increase in the percentage of solids of the muscle was less than that found in the control experiments. However, the control experiments were of longer duration.

In the next five experiments, whole blood amounting to 0.5 per cent of the body weight was removed from the femoral arteries at six hour intervals until the animals died. The samples were obtained before the first bleeding and after the blood pressure had been reduced to a low level. The level of the mean blood pressure at the time that the second series of samples were obtained varied from 0 to 63 mm. of mercury. The average decrease in hemoglobin was 8 per cent of that of the control period. The content in solids of the blood was changed from 19.1 to 19.5 per cent, that of the muscle from 24.5 to 25.2 per cent and that of the skin from 45.8 to 49.5 per cent. There was a smaller increase in the percentage of solids in the muscle in these experiments than in the control experiments in which simply the effects of prolonged barbital anesthesia were determined. The alterations in the skin and muscle

were approximately the same as in the experiments in which the bleedings were at one hour intervals

In the succeeding four experiments, blood plasma equal to 0.5 per cent of the body weight was removed at one hour intervals until death resulted. Samples were obtained before the first removal of the plasma and shortly before the termination of the experiments, at which time the mean blood pressure varied from 15 to 50 mm of mercury. The average increase in hemoglobin was 36 per cent of the figures for the control periods. The content in solids of the blood was altered from 19.1 to 23.2 per cent, that of the muscle from 25.1 to 26.5 per cent, and that of the skin from 48.7 to 46.8 per cent.

In the next four experiments, blood plasma amounting to 0.5 per cent of the body weight was removed at six hour intervals until the animal died. Samples were obtained at the beginning and shortly before the termination of the experiments, at which time the mean blood pressure varied from 0 to 57 mm of mercury. The average percentage in hemoglobin was 24 per cent higher at the termination of the experiments. The average content in solids of the blood was altered from 19.3 to 22.1 per cent, that of the muscle from 24.6 to 25.1 per cent and that of the skin was practically unchanged.

In the succeeding four experiments, the effects of mild trauma to an extremity on the content in solids or in water were determined. The interval of time that elapsed between the initiation of the trauma and the reduction of the blood pressure to the desired level varied from twenty-two to thirty-one hours. Specimens of blood, muscle and skin were obtained before the institution of the trauma and after the mean blood pressure had been reduced to levels varying from 42 to 90 mm of mercury. The average percentage in hemoglobin was 23 per cent higher at the termination of the experiments than at the beginning. The average content in solids of the blood was increased from 19.4 to 23.6 per cent, that of the muscle from 25.3 to 26.5 per cent, and that of the skin decreased from 36 to 35 per cent. The alteration in the content of solids of blood and muscle was slightly greater in these experiments than in those in which blood plasma was removed at six hour intervals. The duration of the two types of experiments was approximately the same.

In the next four experiments, the effects of trauma to the intestines were studied. The time that elapsed between the beginning of the trauma and the reduction of the pressure to the desired level varied from two hours and thirty minutes to seven hours. Specimens of blood, muscle and skin were obtained before the initiation of the trauma and after the mean blood pressure had been reduced to levels varying from 32 to 57 mm of mercury. The average percentage in hemoglobin was 48 per cent higher at the termination of the experiments than at the beginning. The average content in solids of the blood was altered from 20.1 to 22.8 per cent, that of the muscles from 24.3 to 25.5 per cent and

that of the skin from 40.4 to 40.7 per cent. The alteration in the content of solids of the muscle was approximately the same as in the experiments in which plasma was removed at one hour intervals. The duration of the two types of experiments was approximately the same.

In the succeeding four experiments, the effects of burns were studied. The time that elapsed between the beginning and the end of the experiments varied from fourteen to twenty hours. The mean blood pressure at the time the second series of samples were obtained varied from 0 to 86 mm. of mercury. The average content in solids of the blood changed from 21.5 to 23.8 per cent, that of the muscle from 26.8 to 28.3 per cent, and that of the skin from 42.0 to 49.1 per cent. The alteration in the percentage of solids of the muscle was the same as that in the experiments in which plasma was removed at one hour intervals and approximately the same as that found in the experiments in which an extremity or the intestines were injured.

The results of all of these experiments are given in table 2.

The percentage alterations in the average amount of solids of the blood, muscles and skin that were produced by the various procedures are given in table 3.

TABLE 2—*The Percentage in Solids of Blood, Muscle and Skin Before and After the Various Procedures*

Procedure	Experiment	Time Samples Were Obtained	Mean Blood Pressure, mm. Hg	Hemoglobin per cent	Per Cent in Solids			Comment
					Blood	Muscle	Skin	
Controls effects of barbitaral anes- thesia and water deprivation	1	Control	137	60	17.2	21.7	31.2	46 hours between samples
	2	End of experiment	96	73	19.4	22.8	34.0	47 hours between samples
		Control	160	70	19.0	24.1	38.9	
	3	End of experiment	168	82	20.0	25.7	44.5	46 hours between samples
		Control	145	66	19.0	22.0	28.7	
	4	End of experiment	116	78	20.6	22.4	30.0	46 hours between samples
		Control	145	66	17.0	25.2	34.3	
	5	End of experiment	148	78	20.8	24.8	39.5	26 hours between samples
		Control	122	66	18.4	25.2	52.5	
	Aver- ages	End of experiment	122	74	19.3	27.6	48.2	
Removal of whole blood, 0.5%, every hour	1	Control	136		20.6	26.5	43.8	5% of body weight
	2	End of experiment	20		20.5	26.3	44.0	4.5% of body weight
		Control	160	75	19.4	26.2	43.4	
	3	End of experiment	64	67	17.0	27.0	49.0	5% of body weight
		Control	122		15.5	22.4	30.5	
	4	End of experiment	44			22.8	31.1	5% of body weight
		Control	152	87	20.0	23.9	35.2	
	5	End of experiment	64	73	19.5	24.2	41.6	3% of body weight
		Control	115	78	18.1	24.4	52.8	
	Aver- ages	End of experiment	36	65	16.4	25.5	56.1	
Removal of whole blood, 0.5%, every six hours	1	Control	140	87	21.5	25.1	44.0	2.5% of body weight
	2	End of experiment	Dead			26.7	46.1	2% of body weight
		Control	156	87	22.0	26.6	43.8	
	3	End of experiment	10		24.5	25.9	43.5	3% of body weight
		Control	126	53	15.3	22.1	60.4	
	4	End of experiment	50	48	15.0	24.0	64.4	3.5% of body weight
		Control	124	70	17.8	24.8	38.5	
	5	End of experiment	60	65	17.5	24.1	46.6	4% of body weight
		Control	129	84	21.1	24.1	42.7	
	Aver- ages	End of experiment	63	77	21.1	25.2	47.0	
		Control			19.1	24.5	45.8	
		End of experiment			19.5	25.2	49.5	

TABLE 2—*The Percentage in Solids of Blood, Muscle and Skin Before and After the Various Procedures—Continued*

Procedure	Experiment	Time Samples Were Obtained	Mean Blood Pressure, Mm Hg	Hemoglobin per Cent	Per Cent in Solids			Comment
					Blood	Muscle	Skin	
Removal of plasma, 0.5%, every hour	1	Control	143	63	17.2	23.8	46.4	2.5% plus 1% whole blood
		End of experiment	50	63	18.7	24.4	45.6	
	2	Control	164	71	20.0	24.4	45.4	2.5% plus 1% whole blood
		End of experiment	15	118	24.3	25.3	42.5	
	3	Control	123	74	19.8	25.0	53.9	3.5% plus 1% whole blood
		End of experiment	42	105	24.7	25.6	53.8	
	4	Control	145	80	19.4	27.3	49.2	3.5% of body weight
		End of experiment	50	99	25.2	30.5	45.4	
Average		Control			19.1	25.1	48.7	
		End of experiment			23.2	26.5	46.8	
Removal of plasma, 0.5%, every six hours	1	Control	124	68	16.9	24.0	55.1	2% of body weight
		End of experiment	45	86	20.2	24.5	58.3	
	2	Control	138	79		22.9	55.9	2% of body weight
		End of experiment				23.6	59.1	
	3	Control	148	81	21.1		70.0	2% plus 0.5% whole blood
		End of experiment	20	106	24.9		54.9	
	4	Control	140	81	20.8	27.7	51.0	3.5% of body weight
		End of experiment		93	22.4	28.0	41.7	
	5	Control	145	66	18.2	23.6	50.7	2.5% of body weight
		End of experiment	57	81	20.8	24.2	48.3	
Average		Control			19.3	24.6	65.7	
		End of experiment			22.1	25.1	65.6	
Leg trauma	1	Control	140	103	22.3	28.4	40.3	25 hours between trauma and termination
		End of experiment	42	115	25.2	27.3	28.4	
	2	Control	145	68	19.2	23.8	31.3	31 hours between trauma and termination
		End of experiment	90	89	23.4	28.3	37.3	
	3	Control	160	88	21.3	26.0	46.2	22 hours between trauma and termination
		End of experiment	48	112	26.2	28.0	42.4	
	4	Control	139	53	14.7	22.8	26.2	22 hours between trauma and termination
		End of experiment	61	68	18.6	22.3	31.7	
Average		Control			19.4	25.3	36.0	
		End of experiment			23.6	26.5	35.0	
Intestinal trauma	1	Control	165	76	20.1	25.6	47.0	Trauma of 7 hours' duration
		End of experiment	49	125	24.2	27.7	52.1	
	2	Control	160	71	19.1	26.1	46.1	Trauma of 5 hours' duration
		End of experiment	57	106	22.8	27.2	37.2	
	3	Control	116	62	19.7	21.1	29.2	Trauma of 2½ hours' duration
		End of experiment	40	70	17.6	21.8	27.5	
	4	Control	140	85	21.5	24.5	39.3	Trauma of 3½ hours' duration
		End of experiment	22	105	26.6	27.4	45.8	
Average		Control			20.1	24.3	40.4	
		End of experiment			22.8	25.5	40.7	
Burns	1	Control	165	78	21.2	26.7	42.5	14 hours between burn and death
		End of experiment			22.5	28.9	55.8	
	2	Control	120	57	18.8	26.0	49.7	16 hours between burn and death
		End of experiment			18.5	27.1	52.5	
	3	Control	155		22.6	26.6	44.1	20 hours between burn and termination
		End of experiment	86		27.9	28.5	40.0	
	4	Control	160		2.4	28.0	41.7	17 hours between burn and termination
		End of experiment	60		26.1	28.6	48.1	
Average		Control			21.5	26.8	42.0	
		End of experiment			23.8	28.3	49.1	

TABLE 3—*The Percentage Alterations in the Average Per Cent in Solids of Blood, Muscle and Skin That Were Produced by the Various Procedures*

Procedure	Percentage Alterations		
	Blood	Muscle	Skin
Control experiments on barbital	-10.5	-8.5	-5.7
Removal of whole blood 0.5% every hour	-5.6	-2.0	-7.0
Removal of whole blood 0.5% every 6 hours	-2.1	-2.4	-8.1
Removal of plasma 0.5% every hour	-21.5	-5.6	-3.9
Removal of plasma 0.5% every 6 hours	-14.5	-2.0	
Mild leg trauma	-21.6	-7.7	-2.8
Intestinal trauma	-13.4	-4.9	-0.7
Burns	-10.7	-5.6	-16.9

COMMENT

The analyses of particular interest in these experiments are those on the skeletal muscle. Volkmann⁹ stated that 50.8 per cent of the total water of the body tissues is in muscle. Durig¹⁰ found in animals deprived of water that all of the organs do not lose weight to the same extent. The brain loses the least weight, next comes the kidney, with the heart, liver and muscle increasing in order. Engels¹¹ studied the effects of the administration of sodium chloride on the water content of the various tissues of the body. He used as his controls dogs that had received neither food nor water for four days. After administration of fluids, the muscles increased in weight more than any other tissues except the kidneys. The blood showed the least increase. Of the total amount of water taken up by the tissues of the body, 68 per cent was absorbed by the muscle. Bidder and Schmidt,¹² Bischoff,¹² Volkmann¹² and Voit¹² showed that the skin and muscles not only contain the highest percentage of water, but that they are also the greatest reservoirs for water in the body. In experimental diarrhea produced by magnesium sulphate or senna, Tobler¹³ found that from 25 to 30 per cent of the body weight was lost in a few days, and that skin and muscle suffered 65 per cent of the loss. In his review on anhydremia, Marriott¹⁴ stated "The body possesses an available store of water which exists for the greater part in the muscles and in the skin, and which can be drawn upon to some extent before any considerable degree of desiccation of other parts of the body occurs." The determinations on the skin in the present experiments are probably almost valueless, because it was impossible to be sure in all instances that all of the fat had been removed from its under surface. Fatty tissues contain very little water, and hence any alterations in the amount of fat that was left attached to the skin would change the percentage in water of the sample.

The various procedures produced surprisingly small alterations in the content in solids of skeletal muscle and likewise of all other tissues that were analyzed. The change in the percentage of solids of the skeletal muscle was greater in the experiments in which the animals were anesthetized by barbital and deprived of food and water for periods varying from twenty-six to forty-seven hours than in the experiments

9 Volkmann, A. W., quoted by Engels (footnote 11)

10 Durig, A. Wassergehalt und Organfunction, *Arch f d ges Physiol* **85** 401, 1901

11 Engels, W. Die Bedeutung der Gewebe als Wasserdepots, *Arch f exper Path u Pharmacol* **51** 346, 1904

12 Quoted by Tobler (footnote 13)

13 Tobler, L. Zur Kenntnis des Chemismus akuter Gewichtsstuerge, *Arch f exper Path u Pharmacol* **51** 346, 1904

14 Marriott, W. McKim. Anhydremia, *Physiol Rev* **3** 275, 1923

in which injury was instituted or in those in which whole blood or plasma was removed. It has been shown by Beard and one of us (A. B.)⁸ that the fluid that is lost from the blood stream at the site of injury after mild trauma to an extremity, after trauma to the intestines and after burns has approximately the same composition as the plasma of the blood. There was a loss of plasma in the experiments in which whole blood was removed from the femoral artery. It is mainly the proteins of the blood plasma which maintain the osmotic pressure in the capillaries and serve to counterbalance the filtration force due to the hydrostatic pressure. When plasma is lost from the blood stream as a result either of trauma or of hemorrhage, there is a decrease in the colloids of the circulating blood and hence a lowering of the total osmotic pressure. In view of this, it is not surprising that there is apparently such a small amount of water that passes into the blood stream. The results of these experiments indicate that the same mechanisms operate after hemorrhage and after trauma. They are probably different in degree in that the osmotic pressure in the capillaries is lowered more by the loss of plasma than by the removal of the same amount of whole blood. Associated with trauma is injury to the capillaries, which allows not only water but colloids to pass through their walls. The loss of large amounts of plasma causes a diminution in the capillary pressure and this probably tends to allow fluid to pass into the blood stream in noninjured parts of the body just as in hemorrhage. If this takes place, the increase in pressure in the capillaries probably causes further loss of fluid into the injured area. It is probably for this reason that shock due to trauma is usually more difficult to treat than that due to uncomplicated hemorrhage. After hemorrhage, it is usually simply a matter of restoring the blood volume after the bleeding vessels have been ligated. After trauma, any procedure that increases the hydrostatic pressure in the vessels tends to cause the further loss of fluids through the injured capillaries.

As has been stated previously, the amount of water that left the tissues for the blood stream in these experiments was not great. If it is assumed for the moment that the amount of water that passed from all tissues of the body into the blood stream equalled 2 per cent of the body weight, and this figure does not seem low in view of the present observations, this would represent 200 cc. in a dog weighing 10 Kg. In experiments of the duration of the average experiment reported here, the greater part of the water would be lost in the expired air and a smaller proportion in the urine and feces.

It is of interest that whereas there was usually a slight diminution in the amount of water in the uninjured tissues of the body, there was an increase in the content in water of the damaged tissues. It is believed that this is strong evidence against the possible action of toxic products which produce a general increase in capillary permeability. It is also of

interest that whereas the subcutaneous tissues of a burned area had a great increase in their content in water, the muscle beneath the injured area had a slightly lower content in water than muscle from the opposite nonburned side.

It is believed that these experiments emphasize the importance of the plasma proteins in maintaining a normal blood volume. They indicate that only a small amount of water leaves the tissues for the blood stream when there has been a considerable reduction of the blood plasma.

SUMMARY

The content in water and solids of various tissues of the body has been determined in control experiments and in those in which a low blood pressure had been produced by trauma and burns. The animals were all anesthetized by barbitol and were not given water or food during the experiments. There was little difference in the content in water or solids of the tissues in the control experiments and in those in which injury had been inflicted.

In additional experiments, the content in water and solids of blood, muscle and skin was determined before and after a low blood pressure had been produced by the removal of whole blood, by the removal of blood plasma, by mild trauma to an extremity, by trauma to the intestines and by burns. The results were compared with those obtained in experiments in which the animals were simply given barbitol and left on the table for periods of time varying from twenty-six to forty-seven hours. The analyses of particular importance were those on the muscles, because they contain the greater part of the water in the body. There was a larger loss of water by the muscles in the control experiments than in those in which hemorrhage or injury was studied.

Reasons are given for the belief that hemorrhage and trauma are similar in that in each there is a loss of plasma proteins with a diminution in the total osmotic pressure. After trauma, there is a larger proportional loss of blood plasma and hence a relatively greater diminution in the osmotic pressure. The decrease in the colloids explains the inability of the blood stream to attract more water from the tissues. The main factor which is most likely responsible for the continued low blood pressure after injuries is not a general increase in capillary permeability with loss of fluid all over the body but a loss of blood plasma through the walls of the damaged capillaries.

THE ABSORPTION OF DEXTROSE FROM THE COLON

II A STUDY OF THE EFFECTS OF CHEMICAL EXCITANTS AND OF STIMULANTS ON DEXTROSE ENEMA

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Results obtained by us¹ previously in experiments carried out on dogs indicate that a 5 per cent aqueous solution of dextrose is not absorbed from the colon to any appreciable extent Tap water and physiologic solution of sodium chloride are rapidly and efficiently absorbed As a control in those experiments we exposed the ileum simultaneously to the same solutions in the same dog by using the same technic, and variable but considerable absorption was observed

This study was continued in order to observe the fate of dextrose in enemas made up of equal parts of 5 per cent solution of dextrose and solutions of various chemicals that might possibly act as excitants or stimulants to absorption The fact that a 0.9 per cent solution of sodium chloride was readily absorbed by the large bowel suggested that salt might favor the absorption of dextrose when the two substances are mixed in proper proportions

Goldschmidt² and Fantus³ informed us that the presence of sodium chloride in the intestine increases the absorption of other substances Sodium bicarbonate is another chemical commonly used by surgeons in postoperative enemas Clendenning⁴ stated that sodium bicarbonate and brandy are both beneficial adjuncts to rectal administration Bab-

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These experiments were carried out in the Physiological Laboratory of Northwestern University Medical School, under Dr A C Ivy, head of the Department of Physiology

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3 Fantus, Bernard The Technic of Medication, Chicago, American Medical Association, 1926

4 Clendenning, Logan Modern Methods of Treatment, St Louis, C V Mosby Company, 1928

kin⁵ reported that the activity of the gastro-intestinal tract is markedly increased and may even be doubled by the presence of alcohol

Our experiments in this study were made in order to determine what effect, if any, sodium chloride, sodium bicarbonate and ethyl alcohol might exert on the absorption of a dextrose solution from the colon of the dog. Attention was focused mainly on the nutrient value of the sugar enema and less on the mechanism of absorption. Incidentally, however, it was impossible to disregard entirely some interesting effects that these substances seem to exert on the intestinal mucosa and on the liver. These incidental effects will be considered only briefly in this paper, since we regard that part of the problem as open for further investigation.

METHODS AND TECHNIC

Dogs were used in these experiments as in our previous work. They were prepared and the experiments were carried out exactly as before¹ with two minor alterations in the details.

In the first place the solution to be absorbed was allowed to remain in the ileum and colon for one hour instead of one and one-half hours. This was done because we have found that the maximum rates of absorption in the dog's intestines, large and small, are reached usually in about from twenty to thirty minutes after the solutions are introduced, and that in about one hour the rate of absorption is usually diminishing. Our curves for blood sugar demonstrate this fact. It is interesting to note also that in several instances more than 70 cc of fluid were taken up in one hour by a loop of ileum approximately 18 inches (45.72 cm) in length. Professor Verzar⁶ finds that about 16 cc of water per minute are taken up by the human intestine, or, roughly speaking, about 0.5 cc per foot (30.48 cm) per minute. In many of our experiments this rate of absorption was greatly exceeded by the ileum.

Secondly, another control check was run on the blood sugar by taking in all instances samples of blood from the femoral vein for determinations of sugar in addition to samples from the mesenteric veins of the colon and the ileum. This sample of blood from the femoral vein is representative of the blood sugar content of the general systemic circulation, and is of considerable interest and importance in our interpretations.

Three groups of experiments were performed. In the first group six dogs were used. We mixed equal quantities of solutions of 5 per cent dextrose and 0.9 per cent sodium chloride. We have shown⁷ in an earlier report that the optimum concentration of a dextrose solution, or any other solution that is introduced into the body, is that concentration with the same osmotic tension as a

5 Babkin, B. P. *Die äussere Sekretion der Verdauungsdrüsen*, ed. 2, Berlin, Julius Springer, 1928.

6 Verzar, Professor of Physiology, University of Budapest, Hungary, in a lecture on absorption from the intestine given at Northwestern University Medical School, Oct. 8, 1929.

7 Willems, J. D., and McNealy, R. W. Glucose Solution Its Optimum Concentration for Therapeutic Administration. *Northwest Med.* 28:329, 1929.

physiologic solution of sodium chloride. A 4.5 or 5 per cent dextrose solution is iso-osmotic with a 0.9 per cent salt solution. By beginning with two isotonic solutions, all mixtures of the two in any proportions whatever will still remain at the same osmotic level and be isotonic with the blood and the tissue fluids. The mixture that we used in this group contained 2.5 per cent dextrose and 0.45 per cent sodium chloride. Such a mixture is physiologically normal, and is most likely to be absorbed if absorption of these substances in the colon does take place. Our endeavor was to establish the most favorable circumstances for absorption.

After proper preparation of the narcotized animal, blood samples were withdrawn from three points: the femoral vein, the mesenteric vein of the colon and the mesenteric vein of the lower end of the ileum. Accurately measured quantities of the dextrose-salt mixture, usually 75 cc. were then placed into each of the isolated bowel loops by the methods that we¹ have described in our preliminary report. Twenty minutes later and forty minutes later, samples of blood were again withdrawn from the same places previously mentioned. One hour after the introduction of the solutions their residues were removed, accurately measured and titrated by Benedict's quantitative method for dextrose. Sugar determinations were made on the samples of blood by the Folin and Wu colorimetric method. In both of these procedures it was important that one develop a certain facility and accuracy of technic before the determinations could be called completely reliable, and the marginal error was reduced to a definite constant minimum.

From the figures obtained for the mixed solutions in the intestinal loops, graphs were plotted (of which charts 1, 3 and 5 are typical examples) showing in terms of cubic centimeters the amounts of solution introduced and removed after one hour's exposure to the absorptive possibilities of the bowels, and showing also the amounts of dissolved dextrose introduced and removed in terms of grams. From the figures representing the blood sugar values in the nine samples of blood, graphs were made showing the levels of the blood sugar in the femoral vein and in the mesenteric veins of the ileum and of the colon. Charts 2, 4 and 6 are representative of these graphs. All the charts here reproduced are paired, each pair being made from the same animal in the course of one experiment. Therefore they show conclusively what happened, so far as the sugar is concerned, within the lumen of the bowels and in the blood.

The second group of experiments covers three dogs and differs from the first only in that the substances used were equal quantities of 5 per cent solution of dextrose and 1.5 per cent solution of sodium bicarbonate. From the standpoint of the molecular weight and the freezing point depression of sodium bicarbonate, such a concentration is practically physiologically normal. Charts 3 and 4 are from a typical experiment of this type.

The third group involves four dogs. A mixture of 5 per cent dextrose and 6 per cent ethyl alcohol was used. The experiments were carried out as before. No unified idea exists among authors as to the strength of alcohol that will give optimal results physiologically. From 1 to 12 per cent has been used. A concentration of about 0.75 per cent in the blood stream is required before serious damage results to the blood. With such vague information for a starting point, we decided on a 3 per cent strength of alcohol for this particular type of experiment. The results were quite definite, as will be shown later.

Mention should be made here that we have made no effort to determine the fate of the exciting substances other than the dextrose in the intestines. Nor do we know the amounts of sodium chloride, of sodium bicarbonate or of alcohol that were present in the residual solutions.

EXPERIMENTAL RESULTS

Examination of the charts, which are from typical experiments of each group, will give the clearest idea of the results. Charts 1 and 2 represent dog T, a male, weighing 43 pounds (19.5 Kg). Seventy-five

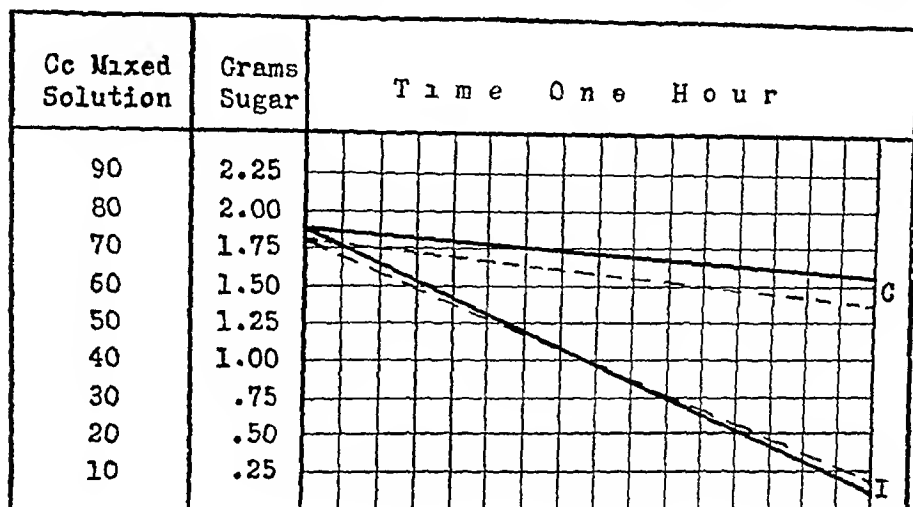


Chart 1—Absorption of a dextrose-saline enema from the colon, C, and the ileum, I. The solid lines represent the solution, the broken lines, dextrose. The left hand column shows the amount of solution in cubic centimeters, the next column, the amount of dextrose in grams.

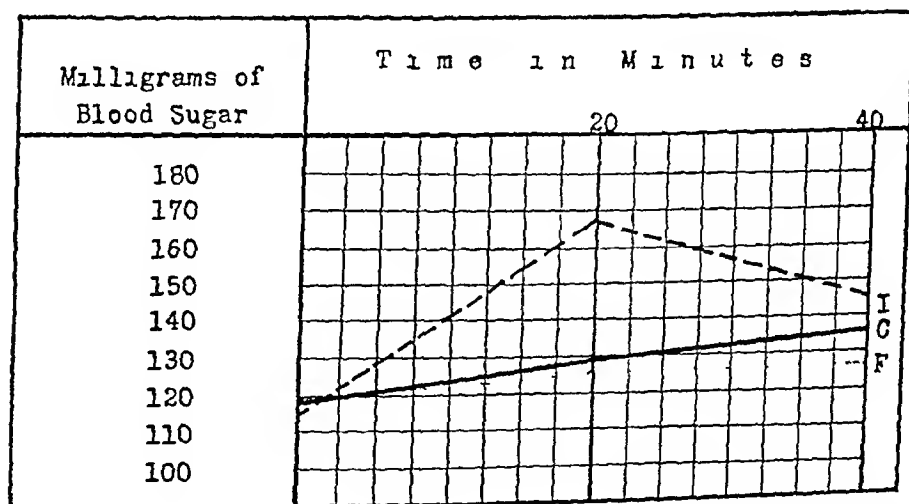


Chart 2—Blood sugar levels, before and after the administration of the dextrose-saline enema, in the colic vein, C, ileal vein, I, and femoral vein, F. The column of figures is the scale on which the blood sugar level is measured.

cubic centimeters of the dextrose-salt mixture, containing 1.79 Gm of dextrose, was introduced quantitatively into each bowel loop. From the ileum we removed 4 cc of residual solution containing 0.14 Gm of dextrose, from the colon, 62 cc containing 1.37 Gm of dextrose. From

the ileum, 71 cc of solution, and 1.65 Gm of dextrose were absorbed, from the colon, 13 cc and 0.42 Gm. A glance at the graphs will aid considerably in visualizing these figures.

Chart 2 shows the observations on the blood sugar in the same experiment. At the beginning of the experiment, the blood sugar values

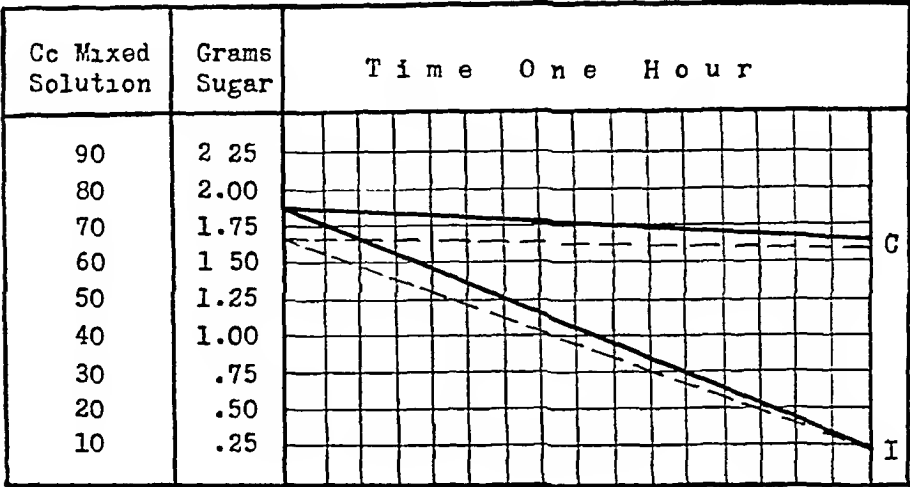


Chart 3—Absorption of a dextrose-sodium bicarbonate enema from the colon, C, and the ileum, I. The solid lines represent solution, the broken lines, dextrose.

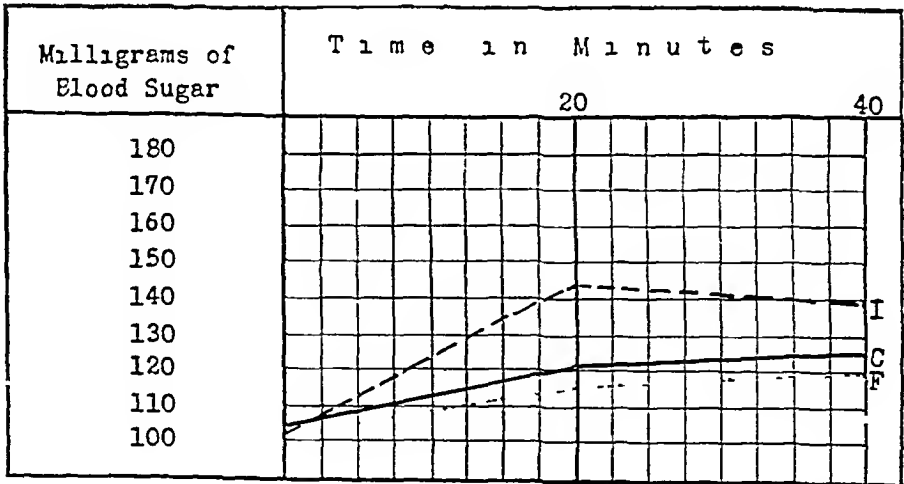


Chart 4—Blood sugar levels, before and after the administration of dextrose-sodium bicarbonate enema, in the colic vein, C; in the ileal vein, I; and in the femoral vein, F.

are seen to be as follows: C, 119 mg; I, 115 mg; F, 120 mg. In twenty minutes these values are, respectively, 129, 166 and 126 mg. At forty minutes, they are 135, 145 and 127 mg. Again a glance at the chart will make clear the meaning of these figures. It shows that there is an obvious reciprocal relation to the observations recorded in chart 1.

Charts 3 and 4 are those for dog Y, a female, weighing 36 pounds (16.3 Kg). In this case 75 cc of dextrose-sodium bicarbonate mixture was introduced, in which there was contained 1.68 Gm of dextrose. One hour later we removed from the ileum 9 cc of solution together with 0.22 Gm of dextrose, from the colon 65 cc and 1.58 Gm of

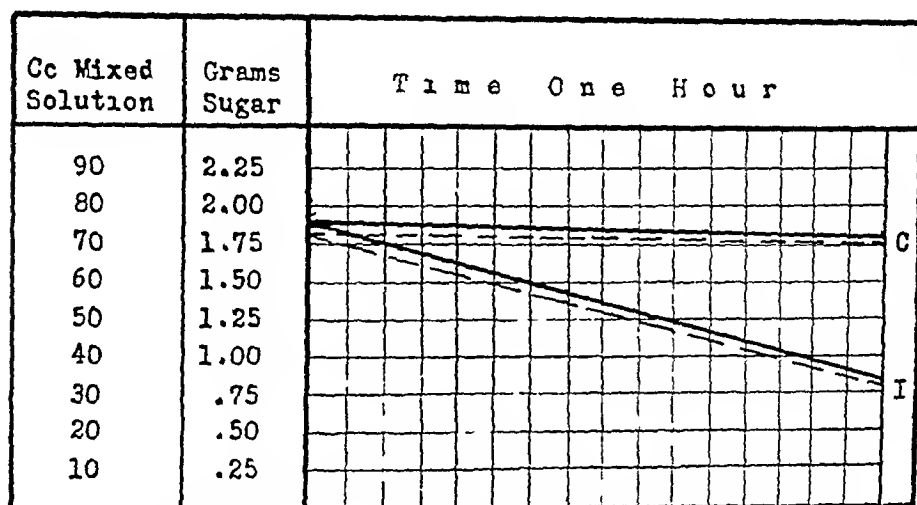


Chart 5—Absorption of a dextrose-alcohol enema from the colon, *C*, and from the ileum, *I*. The solid lines represent the solution, the broken lines, dextrose

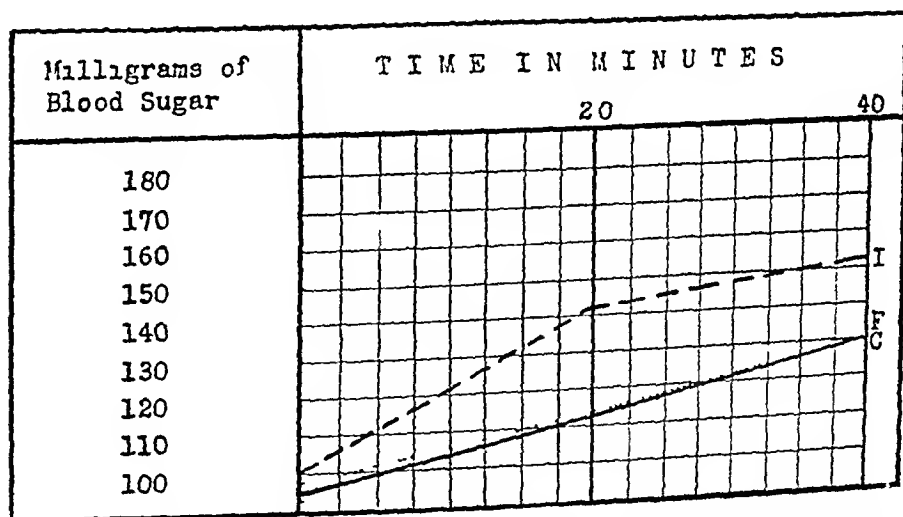


Chart 6—Blood sugar levels, before and after the administration of dextrose-alcohol enema, in the colic vein, *C*, in the ileal vein, *I*, in the femoral vein, *F*

dextrose. The blood sugar values at the outset were *C*, 104 mg, *I*, 102 mg, *F*, 102 mg. At the twenty minute period there were, respectively, 121, 143 and 115 mg, at the forty minute period, 125, 139 and 119 mg.

Charts 5 and 6 show graphically what occurred in dog W, a male weighing 40 pounds (18.1 Kg). In this experiment 75 cc of dextrose-alcohol mixture was used, containing 1.86 Gm of dextrose. There remained in the ileum at the end of the experiment 32 cc of the solution, containing 0.79 Gm of dextrose, in the colon, 71 cc containing 1.78 Gm. The blood sugar values in this experiment were as follows: First samples, *C*, 96 mg, *I*, 100 mg, *F*, 97 mg, twenty minute samples, *C*, 112 mg, *I*, 141 mg, *F*, 113 mg, forty minute samples, *C*, 130 mg, *I*, 152 mg, and *F*, 130 mg.

COMMENT

When we worked out our earlier results¹ with an aqueous solution of dextrose, we were surprised to note that the colon absorbed practically no sugar. We had expected at least a slight absorption. The redoubling of our efforts at accuracy and the elimination of marginal errors only duplicated our observations. When we used tap water or physiologic solution of sodium chloride, it was found that the colon absorbed these substances rapidly. In fact, the colon absorbed salt solution more efficiently than water and did it better than, or as well as, the ileum. Therefore, it appeared interesting to know how the colon would handle a mixture of such an excitant as sodium chloride and such a deterrent as dextrose. Obviously, if conditions within the colon could be kept physiologically as nearly normal as possible and the solutions isotonic one of the three substances, namely, water, dextrose or excitant, or any two of them, or even all three of them, might possibly be absorbed. But—in the words of that peer among modern physiologists, Claude Bernard—why think and wonder when one can experiment and know?

When 75 cc of any solution is introduced into the colon and removed without any absorption taking place, about 95 per cent of the solution can be recovered. About 5 per cent is unavoidably lost in the process of transfer. It is probably safe to state that a loss of more than 5 per cent means absorption. Approximately the same figures hold for the dextrose. In chart 1, it is shown that 17.5 per cent of the fluid and 22 per cent of the dextrose were lost from the colon. This loss was undoubtedly due to absorption. Although the actual amount absorbed was small, it was, nevertheless, too great to be regarded as experimental error.

Dextrose, when absorbed from the colon, can be satisfactorily demonstrated in the portal blood of the vein draining the colon. Once this blood traverses the liver, considerable change may take place. One of the main functions of the liver is the regulation of the blood sugar level in the general systemic circulation. In the process of ingestion of dextrose by the bowel the blood sugar level in the portal blood rises

higher than in the systemic blood, at no time in a physiologically normal procedure can the reverse condition occur. A rise in the blood sugar of the portal blood may be the secondary result of a rise in the general systemic blood sugar, or it may be due to absorption of sugar from the intestine. Indeed, the blood sugar can rise in the colic vein for at least three reasons: absorption of dextrose from the colon; absorption from the ileum which raises the general blood sugar, or because of some change or changes in the liver which releases stored glycogen into the general circulation as dextrose. From any rise in blood sugar in the colic vein must be subtracted the value of the blood sugar in the femoral vein taken at the same moment. The remainder represents the true rise in the colic vein due to absorption of dextrose from within the colon. It was this line of reasoning that showed us the necessity of establishing the general level for systemic blood sugar in the femoral vein each time that any other blood sugar value was taken.

With these points in mind, an examination of chart 2 is exceedingly interesting. At the beginning all three graphs are at approximately the same level, the slight differences being due to unavoidable experimental errors. Then there is a marked rise in the broken line *I*, followed by a less marked decline after absorption in the ileum has reached its peak. The sugar absorbed by the ileum has, to some extent, raised the general level of the blood sugar, because there is a rise in the dotted line *F* as well. The rise in *F* is reflected in the solid line *C*, which has also risen. But the rise in the graph *C* is greater than that in *F*, and that difference can be accounted for only by an actual rise in the blood sugar of the colic vein due to the absorption of dextrose from the colon. The quantity of dextrose absorbed is small, but we have found it repeatedly present in the dextrose-salt experiments. Thus this rise in the blood sugar in this experiment accounts for the loss of dextrose shown in chart 1. It seems plain, then, that the presence of the sodium chloride in this mixture caused the colon to absorb small but definite quantities of dextrose.

In the experiments with dextrose-sodium bicarbonate a slight loss of water is seen in chart 3, but practically no loss of dextrose from the colon. This observation is borne out by the blood sugar curves in chart 4, which show a marked rise in the ileal vein and a parallel rise in the colic and femoral veins, which is simply a rise in the general circulation. There is here no progressive divergence of the graphs *C* and *F* as in chart 2. They remain practically parallel. It is evident that the rise in *C* is merely a reflection of the rise in *F*, and that both are secondary to the rise in *I*. Thus it can be said that there is practically no absorption of dextrose from this mixture in the colon.

In the dextrose-alcohol experiments, as seen in chart 5, there is again no appreciable loss of dextrose from the colon. But the blood sugar levels (see chart 6) rise rapidly in all three curves.

Applying our previous method of reasoning to these observations, we came to the conclusion that the alcohol, reaching the liver probably by way of the ileum, caused some change or changes in that organ which resulted in a marked general hyperglycemia. The nature of this change is not entirely clear. It may be a breaking down of the barrier of the liver to the increase of sugar in the portal blood, or more likely a liberation of dextrose from the stored glycogen in the liver, since the increase of the dextrose in the blood is probably greater than can be accounted for by the absorption of the 1.07 Gm. lost from the ileum. The conclusion seems entirely warranted that alcohol has no demonstrable effect on the absorption of dextrose from the colon. But when the alcohol reaches the liver by way of the ileum, it produces there some change or changes, resulting in a rather sudden marked hyperglycemia.

It is self-evident that experiments of this nature cannot be carried out on human patients. We expect to continue with this work on dogs, and ultimately to adapt the problem in a modified form to the human colon.

SUMMARY AND CONCLUSIONS

1. A 5 per cent solution of dextrose is not absorbed from the colon to any appreciable extent.

2. Tap water and physiologic solution of sodium chloride are rapidly and efficiently absorbed by the colon.

3. A small amount of dextrose can be absorbed from the colon from a dextrose-saline mixture. The sodium chloride influences the absorption of the dextrose.

4. Dextrose is not appreciably absorbed from the colon from a dextrose-sodium bicarbonate mixture.

5. Practically no dextrose is absorbed from the colon when a dextrose-alcohol mixture has been injected. The absorption of the alcohol causes a hyperglycemia in a short time.

6. There is no evidence to show that the dextrose enema is of any practical nutritional value.

CORRELATION OF FUNCTION WITH CAUSE OF DEATH FOLLOWING EXPERIMENTAL INTESTINAL OBSTRUCTION AT VARYING LEVELS *

OWEN H WANGENSTEEN, M D

AND

N LOGAN LEVEN, M D

MINNEAPOLIS

Following complete obstructions of the upper part of the intestine in the dog, life may be prolonged for three or four weeks in a large number of such animals when saline is administered subcutaneously. If the administration of saline is interrupted after five or six days, the animals will often live as long as when saline is administered daily until the death of the animal.¹ When saline is not administered, death usually occurs within three or four days, and an elevation of the blood urea, decrease of the plasma chlorides and an increase in the combining power of the blood for carbon dioxide occur. The administration of saline precludes the development of these chemical changes in the blood. The saline serves as an effectual antidote, not for a toxin absorbed, but for the essential fluids lost by vomiting.

When obstruction is established in the descending colon of a dog, the animal usually survives for a considerable period and, apparently, dies of starvation. Occasionally, death occurs in the first week following such experimental obstruction, we have had two animals that died on the forty-second and fiftieth days postoperatively, following the establishment of obstructions by severing the lower part of the colon.²

When obstruction is established in the lower part of the ileum, dogs survive for a longer period (usually from five to seven days) than do animals with similar obstructions in the duodenum. However, saline does not afford them the protection exhibited by animals with duodenal

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* From the Department of Surgery, University of Minnesota

1 Hausler, R W, and Foster, A C. Studies on Acute Intestinal Obstruction, Arch Int Med **36** 31 (July) 1925. Wangenstein, O H, and Chunn, S S. Studies in Intestinal Obstruction. III Simple Obstruction. A Study of the Cause of Death in Mechanical Obstruction of the Upper Part of the Intestine. Arch Surg **16** 1242 (June) 1928.

2 Wangenstein, O H, and Lynch, F W. Evaluation of X-Ray Evidence as Criteria of Intestinal Obstruction, Proc Soc Exper Biol & Med **27** 674, 1930.

obstruction The length of life of animals with complete ileal obstructions is little greater after the subcutaneous administration of saline than when this is omitted There is at present no satisfactory explanation for the cause of death in simple obstruction of the ileum

TABLE 1—*Anastomosis of Colon to Stomach*

Dog*	Initial Weight Kg	Terminal Weight Kg	Post-operative Duration of Life Days	Subcutaneous Administration of Saline (400 Cc of 1% Solution) Days	Blood Chemistry
1	13.9	8.6	22	0	Essentially normal
2	18.9	10.7	33	0	Essentially normal
3	9.3	8.6	6	0	Essentially normal
4	25.0	16.8	17	0	Terminal CO ₂ combining power 73
5	29.3	14.5	30	0	Essentially normal
6	13.0	9.1	20	0	Essentially normal
7	10.0	7.5	17	2	
8	7.9	7.5	9	4	
9	12.0	8.6	38	3	Essentially normal
Average 21.3 days					

* A fecal impaction just proximal to the anastomosis constituting a simple obstruction occurred in several of these animals

TABLE 2—*Anastomosis of the Ileum to the Stomach*

Dog	Initial Weight Kg	Terminal Weight Kg	Post-operative Duration of Life, Days	Subcutaneous Administration of Saline (400 Cc of 1% Solution) Days	Blood Chemistry
1	17.7	14.3	8	5	Terminal (blood urea nitrogen 114.8 chlorides 181.5)
2	15.5	10.7	24	4	Essentially normal
3	14.3	11.4	5	0	Essentially normal
4	20.5	11.8	56	0	Terminal (blood urea nitrogen 58.8 chloride 165)
5	17.0	11.4	26	0	Normal blood urea nitrogen and chloride
6	21.8	17.3	16	0	Normal blood urea nitrogen and chloride
7	16.6		33	0	
8	25.9	18.2	18	0	
9	21.8		6	1	
10	15.7		16	0	Normal chlorides and blood urea nitrogen
11	11.0	8.3	11	3	Normal chlorides and blood urea nitrogen
Average 19.9 days					

There exists a high degree of correlation between embryology, blood supply and function in the intestine The stomach, duodenum (as far as the papilla of Vater) and the pancreas develop from the foregut Liberal amounts of digestive secretions are furnished by these organs Their source of blood supply is the celiac axis The remainder of the

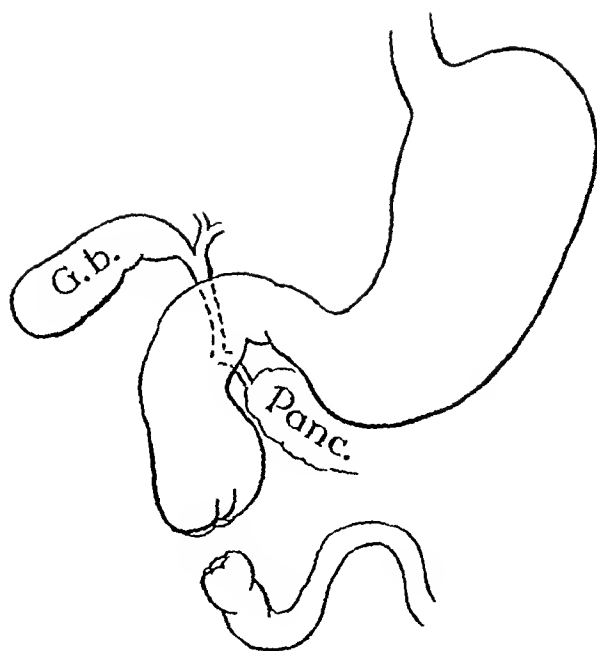


Fig 1—High intestinal obstruction The blood chemistry is as follows high blood urea, low plasma chlorides, alkalosis (high carbon dioxide combining power) Saline is an antidote for fluid lost by vomiting

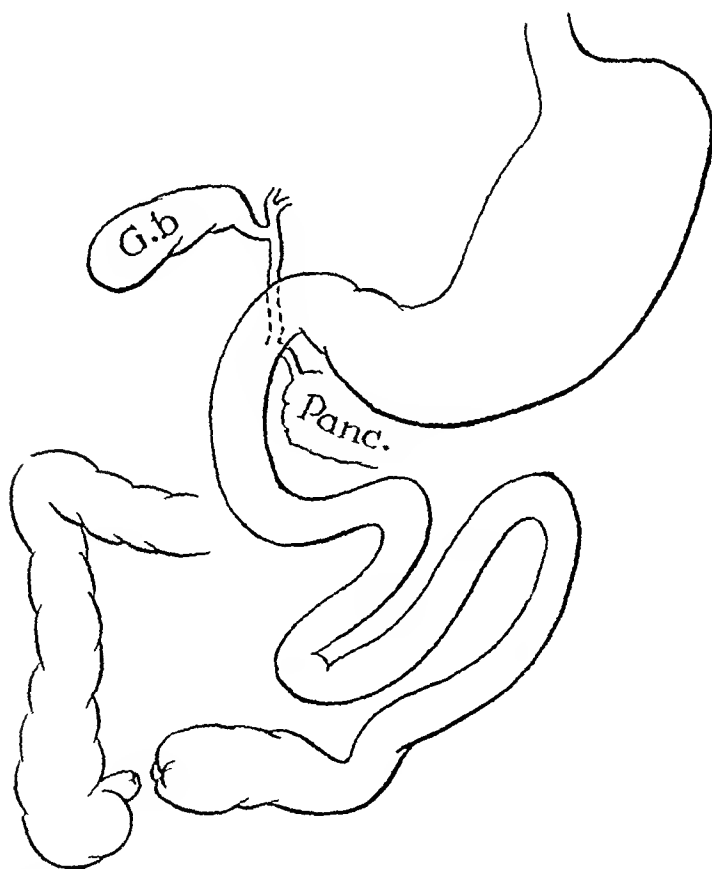


Fig 2—Low ileal obstruction There is no alteration in the blood chemistry, the cause of death is uncertain Saline is not specific

small intestine to the midportion of the transverse colon develops from the midgut, receives its blood supply from the superior mesenteric artery, and has to do with absorption. The remainder of the colon develops from the hindgut, receives its blood supply from the inferior mesenteric artery, and has excretion as its function. In a dog with obstruction low in the colon, the acute obstruction features are frequently absent because the obstruction is beyond the absorptive area.

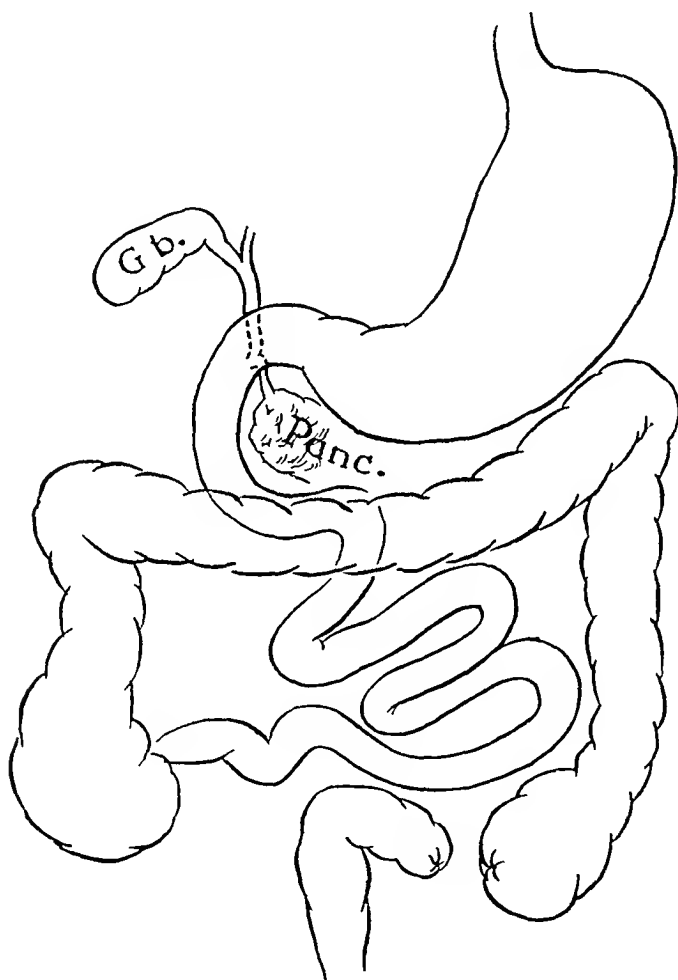


Fig. 3—Obstruction in the lower portion of the colon. There is no alteration in the blood chemistry. The animal dies of starvation or of acute obstruction.

and the accumulation within the bowel is not as great as when the absorptive area is blocked out. Post mortem, such dogs exhibit considerable emaciation. Fecal masses are solidly impacted above the inverted end of the bowel. In those dogs that survive obstruction of the colon for only a short period interference with absorption due to edema and other changes in the proximal wall of the bowel probably

occurs, permitting distention and acute obstructive phenomena to dominate the picture. When the obstruction is established in the lower part of the ileum in the midabsorptive area of the intestine, the picture of acute obstruction and distention predominates.

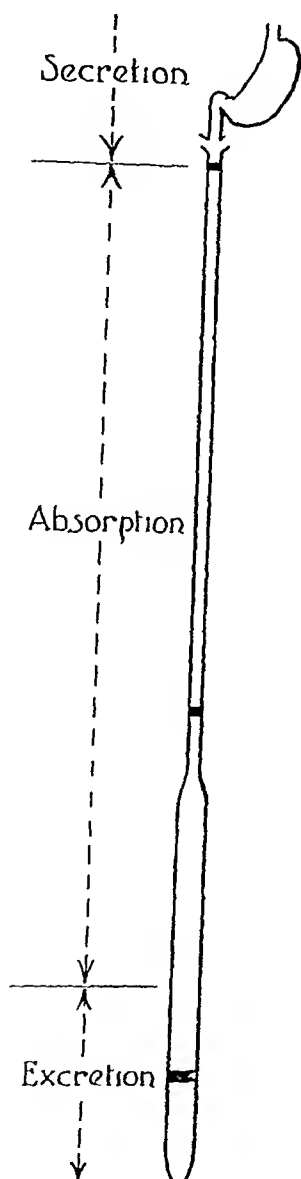


Fig 4—Intestinal tract conceived of as a long straight tube in which the dark lines represent obstructions at the levels already described in the three previous figures. The important factors are (1) loss of essential fluids by vomiting, (2) absorption, (3) distention, especially as related to the blood supply.

In explaining the death of an animal with this type of obstruction, the intestine may be conceived of as a long tube with obstruction in the midabsorptive area. Only the fluid at the upper end can be vomited, the lower portion being more or less continuously full and distended.

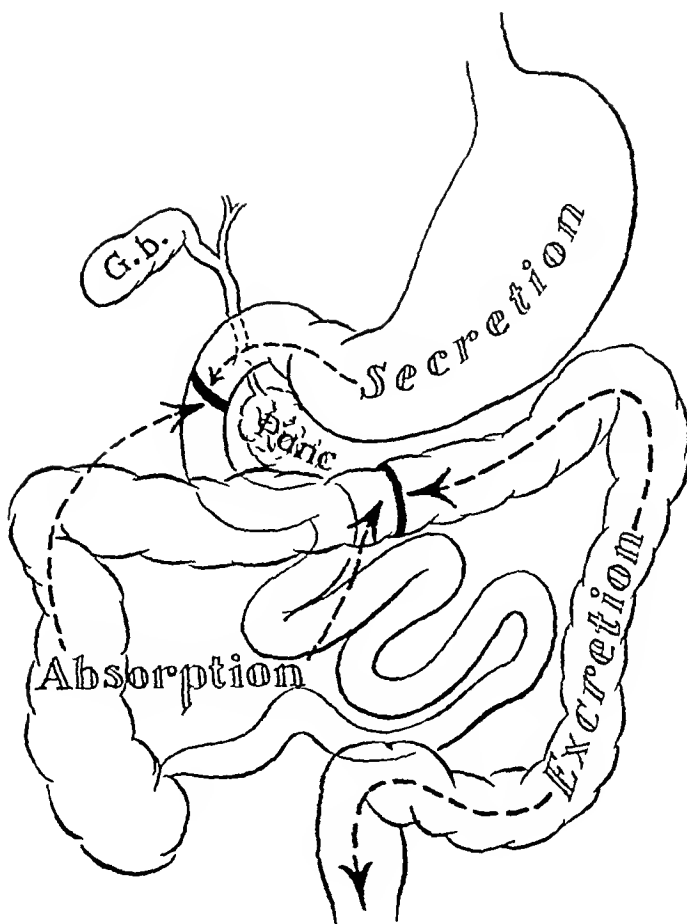


Fig 5—Schematic drawing to illustrate the relation of function in the intestinal tract to the types of obstruction already described

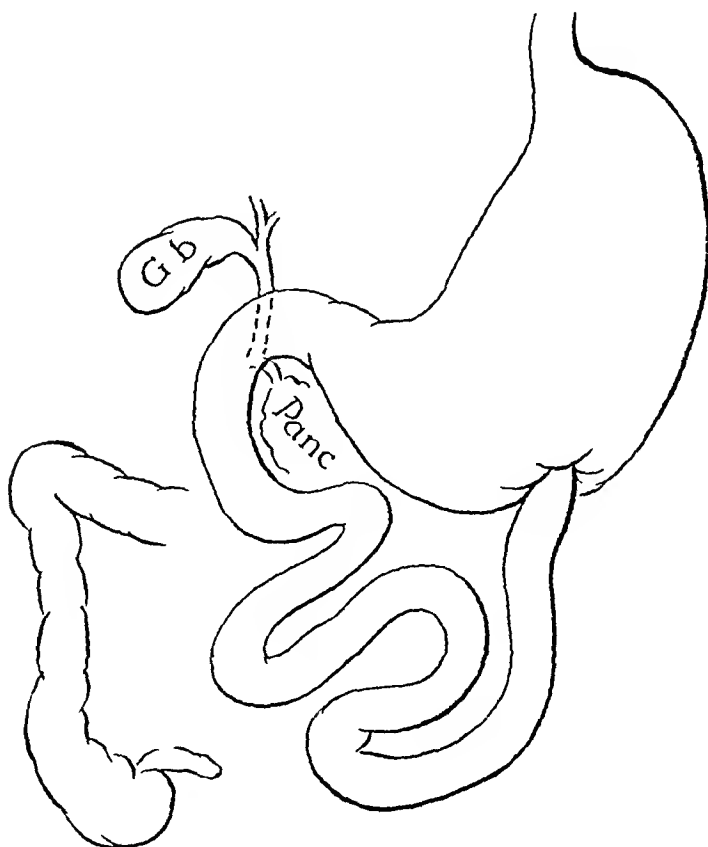


Fig 6—Anastomosis of the terminal ileum to the stomach in which the distal end of the ileum is inverted This is also an obstruction with only the oral end open but with the distal ileum opening into the stomach, from which point its content can easily be evacuated by vomiting

With the increasing accumulation of gas and fluid in such a long tube, the lower reaches of the occluded segment probably partake of the characteristics of strangulation obstruction in which deprivation of the blood supply and necrosis of the wall of the bowel obtain. The ileum also has not as rich a blood supply as have more proximal segments of the small intestine.³

On the premise that the absorptive area is partially blocked out in ileal obstructions, permitting of greater damage to the wall of the bowel, we have anastomosed the terminal end of the ileum to the side of the stomach, permitting the return of the accumulated fluid in the lower reaches of the obstructed segment to the stomach, from which point it is more easily vomited. Such an obstruction was established in eleven dogs. (A few other animals in which this same procedure was performed were excluded from consideration because of the occurrence of peritonitis.) One animal survived the procedure fifty-six days and was in fairly good health, though vomiting daily until the fifth postoperative week, from which time a steady decline occurred. The average period of survival was 19.9 days. Studies of the blood chemistry were made on the animals in this group, with the exception of the blood of dogs 1 and 4, in which there was a terminal rise of blood urea and decrease of blood chlorides, the blood was normal.

In nine other dogs the terminal portion of the descending colon was severed, the distal end being inverted and the proximal end anastomosed to the stomach. The longest period of survival among this group was thirty-three days, with an average of twenty-one and three-tenths days. No change was observed in the blood chemistry values.

In another group of experiments an attempt was made to determine whether a preliminary enterostomy would not prolong the survival period after the establishment of simple obstruction low in the ileum, it being assumed that the ileum would accommodate itself to the absorption of water following exclusion of the colon, which apparently occurs in human beings. Unfortunately, however, dogs stand ileostomy poorly and are poorer risks for experiments on intestinal obstruction than are other normal animals.

The increased survival period (fifteen and nine-tenths days) in the group of dogs in which the end of the ileum was anastomosed to the stomach over that observed (from five to seven days) in dogs with simple obstruction in the lower part of the ileum serves to emphasize

³ Morton, J. J. The Difference Between High and Low Intestinal Obstruction in the Dog, *Arch. Surg.* **18** 1119 (April) 1929.

the significance of the mechanical factors (length of tube and blocked absorption) in the cause of death in low ileal obstructions. Roentgenograms of the abdomen of dogs with several ileal obstructions did not uniformly demonstrate the accumulation of large amounts of gas and fluid in the proximal loops, but greater opportunity for injury of the mucosa would appear to obtain in low ileal obstructions than is observed in duodenal obstructions because of the greater length of the peristaltic rushes.

A REVIEW OF UROLOGIC SURGERY

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LOS ANGELES

(Concluded from p 526)

URETER

Calculi—Cathcart²⁷ reported a case of ureteral stone of unusual size and weight. A man, aged 48, had had appendectomy for severe pain in the right side of the abdomen. During convalescence the same type of pain continued as before operation. Two years later a diagnosis of right ureteral stone was made, and after two attempts the stone was successfully removed. Five years later the abdominal pain again appeared on the right side. For six months the patient had had an uncomfortable, heavy feeling in the right lower portion of the abdomen. A roentgenogram of the kidney and urinary bladder revealed a shadow extending from the transverse process of the third lumbar vertebra to the wall of the bladder. At operation the kidney was freed from its bed and the pedicle was ligated and left loose in the wound. Through a right lower abdominal incision the ureter was cut off close to the wall of the bladder, and the kidney and ureter were delivered. The kidney was practically destroyed, it was hydronephrotic and infected secondarily. There was marked dilatation and infection of the ureter which contained the stone. The entire specimen of kidney, ureter and stone weighed 290 Gm.

In the literature there were only four reports of cases of unusually large ureteral stone. The stone varied in length from 7.5 to 19 cm.

²⁷ Cathcart, Edward. Ureteral Stone of Unusual Size, Proc Staff Meet, Mayo Clin 5:117 (April 30) 1930.

and in weight from 44 to 54 Gm. The largest stone measured 19 cm in length and weighed 52 Gm. The stone in the case reported by Cathcart measured 19 cm in length and weighed 90 Gm.

Deaver and Burden²⁸ reviewed 113 cases of the stone in the ureter. In 66 instances operation was performed, and in 47 treatment was carried out by cystoscopic methods. In 98 of the cases the stone was in the lower part of the ureter, a position favorable for cystoscopic manipulation unless certain contraindications are present.

A stone that has remained for a considerable time in the upper part of the ureter, usually at the ureteropelvic juncture, is firmly fixed, obstructs the passage of a catheter, causes rapid and progressive impairment of renal function and is not amenable to cystoscopic manipulation. Removal of the obstruction should be by ureterolithotomy or by pelvolithotomy. A stone seldom lodges in the middle third of the ureter; if it is in this position the procedure for its removal depends on the acuteness of the symptoms and the condition of the kidney above it. Surgical removal of a stone in this position, although a little more difficult to perform, is preferable to cystoscopic manipulation.

Before removing a ureteral stone surgically, it is essential to know (1) that an accurate diagnosis has been made, (2) the urologic status of the opposite kidney, (3) that coexistent extra-urinary disease has been eliminated or taken into consideration, and (4) that sufficient preoperative preparation has been carried out. In the event of certain complications in the removal of a stone from the ureter, particularly postoperatively, general surgical training is of decided advantage in restoring the patient to health. Ureterolithotomy through an extra-peritoneal approach is the operation of choice for stone in the ureter. To approach the upper third of the ureter the incision is made in the loin, as for nephrectomy. This incision permits possible manipulation of the stone back into the pelvis of the ureter from which its removal may be accomplished with less trauma than from the ureter proper, and renders the kidney available for inspection. The incision may be extended to care for a stone in the middle third of the ureter. The latter may be approached through an incision to the lateral side of the rectus muscle when it is necessary to be more careful in working down toward the ureter by displacing the peritoneum toward the median line. It should be remembered that the ureter is often closely adherent to the peritoneum and, in the dissection, is carried forward with it. Access to the lower part of the ureter may be obtained through an incision to the lateral side of the rectus muscle or by an incision just

²⁸ Deaver, J. B., and Burden, V. G. The Surgical Management of Stone in the Ureter, *Ann. Surg.* **91**: 85 (Jan.) 1930.

above Poupart's ligament. In this position the peritoneum is easily reflected and the base of the bladder is exposed. Manipulation may be difficult because of the depth of the wound. The ureter should be identified and traced down to its juncture with the bladder. When the stone has been located, it is preferable to work it into another position in the ureter, so that the longitudinal incision for its removal will not be placed in the inflamed tissues of the ureter surrounding a lodged stone. Disposition of the ureteral incision is optional. It may be left open or it may be closed by several interrupted sutures, the results being equally satisfactory. A drain must be placed down to it because there is usually some leakage of urine for several days. When there is much infection above the stone it is better not to suture the ureteral incision because of the benefit derived from free urinary drainage.

Functional Disturbance —T Trattner²⁹ considered the behavior of the ureter and presented an easily applied method for the recognition of functional ureteral disturbances. The methods of studying ureteral activity may be classified as direct and indirect ocular observation, electrographic and graphic. Studies have also been conducted with the fluoroscope either during or after the injection of opaque solutions, a method which has been subject to criticism.

T Trattner's graphic method permits the recording of ureteral activity practically without obstructing urinary escape. The method is adaptable to the intact unexposed ureter of man, as well as to the exposed or excised ureter of an animal and is of minimal inconvenience to both patient and operator. Ureteral contractions which pass the entire length of the ureter may be classified as complete, those which arise in the renal pelvis but disappear before reaching the bladder, as incomplete, and those which are confined to a small segment of the ureter, as local. The manometer records the complete, as well as many of the incomplete, contractions, and when the latter immediately follow the former the character of the waves is frequently bigeminal or trigeminal. Manometric tracings have been taken in the following conditions: normal ureter, hydro-ureter and hydronephrosis, lithiasis, after uretero-lithotomy or the spontaneous passage of ureteral stones, cord bladder, bilateral complete duplication of ureters with simultaneous records of all ureters, and ureteritis of various degrees, tuberculous and non-tuberculous.

Manometric tracings are of clinical value in detecting early and late disturbances of ureteral function, in diagnosing dilated ureter and

²⁹ Trattner, H. R. Ureteral Activity in Some Pathologic Conditions, *Arch Surg* **17** 968 (Dec) 1928.

pelvis without opaque studies, in deciding into which ureter to inject an opaque solution when various other examinations disclose no difference between the two sides, and in knowing whether the ureter is involved in tuberculosis, calculous disease or tumor. These studies also permit the classification of ureteritis into three groups according to the degree of ureteral activity. Relief of symptoms in patients who have ureteritis or ureteropyelitis appears to occur simultaneously with the recovery of ureteral activity. Aggravation of the disease seems to be concomitant either with hyperactivity or with the loss of peristaltic contractile ability. Trattner stated that the method is not completely efficient in diagnosis, but that it is an additional diagnostic aid.

Elongation—Vermooten,³⁰ in carrying out experimental work on ureteral stricture observed that partial obstruction of the ureter caused its elongation. He attempted to correlate this fact with ureteral kinks and tortuosities as well as with the elongation of the ureter which may be present in ptosed kidneys. In dogs the tortuosity of the ureters was one of the earliest changes noted after the production of a low ureteral stricture. This was associated with so mild a degree of ureteral dilatation that it could be overlooked if it were not compared with the original ureterograms. In view of the large variation in the normal diameter of the ureteral lumen it is suggested that an indication of elongation of the ureter should mean ureteral obstruction of some kind with slight ureteral dilatation, which is difficult to distinguish from what may be considered the normal limits of the organ.

Ectopia—Sargent³¹ reviewed 186 reported cases of ureteral ectopia. 123 of the patients were females and 63 males. A total of 103 operations was performed on 86 females and 5 males. Nephrectomy was performed in 22 cases, in 11 of these the entire kidney was practically functionless. In 10 cases the kidney had a double pelvis, the lower half draining normally into the bladder and being apparently normal. In the 16 cases in which heminephrectomy was performed the part of the kidney not removed was noted as sufficiently normal to warrant saving. The clinical picture presented by the 5 men treated surgically was that of disease of the upper urinary tract. Either nephrectomy or heminephrectomy was performed, and all the patients were reported cured. Of the 33 females completing the group in which nephrectomy or heminephrectomy was performed, cure of urinary incontinence was consistently reported. Forty-nine operations of a conservative type were

³⁰ Vermooten, Vincent. The Elongation of the Ureter, *J. Urol.* **23** 427 (April) 1930.

³¹ Sargent, J. C. Ureteral Ectopia, *J. Urol.* **23** 357 (March) 1930.

performed Vaginal implantation of the dissected lower end of the ureter into the floor of the bladder was done in 26 cases. Judging the result by the cure of incontinence, 14 operations were reported as successful, and 8 as failures, the result of 4 operations was not noted. Suprapubic implantation of the ureter was performed in 8 cases, in 7 it was successful and in the remaining case the result was not recorded. Two of the suprapubic implantations were done transperitoneally, and 4 extraperitoneally, the method of 2 of the operations was not mentioned. In 12 cases various attempts were made to effect an opening between the ureter and bladder *in situ*.

Nephrectomy, except for its surgical mortality, promises absolute cure in ureteral ectopia and is indicated when the entire kidney is rudimentary or functionless from disease. For male patients especially, the additional removal of the entire ureter, when enormously dilated and tortuous, is advisable. Heminephrectomy is curative, comparatively safe and the procedure of choice when the portion of a double kidney drained by the ectopic ureter is rudimentary or functionless from disease and the remaining part is normal and functionally valuable. Dilatation or infection of the ectopic ureter especially recommends this radical procedure. The value of vaginal implantation of the ectopic ureter into the bladder, although usually curing incontinence, has not been proved so far as the conservation of renal function is concerned. It should be limited to cases in which there is neither dilatation nor infection of the ectopic ureter. Results of vaginal ligation of the ureteral end have not been satisfactory.

[ED. NOTE.—The association of ectopic ureter with disease of the upper urinary tract makes the condition especially amenable to treatment by nephrectomy or heminephrectomy, if the case is suitable. In dealing with the usual infection of the upper urinary tract, ureterectomy is seldom necessary. As was pointed out by Latchem, in exceptional cases a low ureteral obstruction (from calculus or otherwise) with dilatation and suppuration above may create conditions which call for excision of the ureter. Sargent showed that an ectopic ureter is one that frequently needs resection.]

Low ureteral ligation, sometimes employed with impunity when tumors of the bladder around the ureteral orifice are resected, cannot often be used in cases of ectopic ureter, because the ureteritis and renal infection above would result in pyoureter and pyonephrosis. For the same reason, reimplantation operations, which all too frequently fail under any conditions, however ideal, are particularly liable to disastrous results if carried out with an ectopic ureter.

Sargent's review brings out well the fact that nephrectomy and heminephrectomy with excision of the ureter are the procedures of choice in dealing with ureteral ectopia.]

Davis³² stated that ectopic ureter with urethral implantation and without incontinence is rare in the female and presents a difficult diagnostic problem. If the voided urine is purulent but clear urine is obtained from both ureters and there is no infravesical obstruction or lesion of the bladder to explain the pyuria, ectopic ureter with urethral implantation should always be suspected. The proper treatment is nephrectomy in the case of a single kidney and heminephrectomy in the case of a double kidney, with ureterectomy if the ureter fails to drain well.

Hemorrhage—Vynalek³³ stated that severe hemorrhage following ureteral meatotomy is rare, but that troublesome bleeding occurs more often than is generally reported. He cited a case in which severe hemorrhage followed the passage of a ureteral calculus with an apparent increase of the sharp splitting of ureteral meatotomy, necessitating suprapubic cystotomy to control hemorrhage. Had it been possible to visualize the point, the bleeding in this case could probably have been controlled through cystoscopic procedures.

Experimental work on dogs showed that severe hemorrhage can occur following ureteral meatotomy. Severe bleeding following meatotomy with scissors should be controlled immediately by high frequency electrodes. Persistent hematuria, even though not marked following any intravesical cystoscopic procedure should, unless contraindicated, be treated by frequent lavage to prevent clotting.

BLADDER

Rupture—De Tarnowsky³⁴ reviewed and analyzed all cases of ruptured bladder in Cook County Hospital, Chicago, during the years from 1926 to 1929. To those were added private cases and cases from the Ravenswood Hospital, about fifty in all.

Less than 5 per cent of ruptures of the bladder were caused by or accompanied by fracture of the pelvis. Cystoscopic examination gave negative results if in extraperitoneal rupture the tension of the

³² Davis, D. M. Urethral Ectopic Ureter in the Female Without Incontinence, *J Urol* **23** 463 (April) 1930.

³³ Vynalek, W. J. Severe Hemorrhage Following Ureteral Meatotomy, *J Urol* **24** 111 (July) 1930.

³⁴ de Tarnowsky, George. Rupture of the Bladder, *J A M A* **95** 476 (Aug 16) 1930.

extravesical fluid equaled that within the bladder, or if the rent in the serosa and muscularis was overlapped by a fold of mucosa

De Tarnowsky concluded that a large percentage of the accidents reported occurred in cases of overdistended bladders, lying against the anterior abdominal wall, this viscus will burst without any trauma to the bony pelvis. Pain in the lower portion of the abdomen, vesical tenesmus, blood-stained urine or inability to urinate should be sufficient to indicate immediately to the surgeon a probable lesion of the bladder. The average mortality from such lesions, although unquestionably increased by coincident injuries to other organs or tissues, is still too high because primary diagnoses are not being made frequently enough. Rupture of the bladder is as much a surgical emergency as an acute condition in the abdomen, and delay in operating is equally dangerous. Closure of the tear by suture, prevesical or culdesac drainage and catheter à demeure are the three essential operative steps. In individual cases the surgeon may have to modify this technic.

Diverticulum —Schacht and Crenshaw³⁵ stated that diverticula are not often found in the bladder of female patients, the ratio of female to male patients is approximately 3:97. In the group of eighteen women with diverticula, thirteen were found to have true diverticula, and five false diverticula. Three patients had urethral caruncle, and one patient a cyst, 1.2 cm. in diameter, at the neck of the bladder. Of the false diverticula, one was the result of injury at childbirth and the other four were the results of operative procedures in the pelvis and abdomen. Symptoms are usually in proportion to the associated infection of the bladder and complications such as vesical calculus or neoplasms of the bladder. Approximately 70 per cent of the women with this condition are between the ages of 35 and 65.

Tumor —Hamer and Mertz³⁶ stated that angioma of the bladder is rare. It is probably often a slowly growing, congenital tumor. The patients usually are children and young adults, almost half of the reported cases occurring during the first and second decades of life. Frequently the tumor has a rough surface with bluish-black or violet areas as viewed through the cystoscope, indicating its vascular structure. Fulguration is applicable only to the smaller tumors, surgical removal is possible before the surrounding structures are invaded. If removal is accomplished, cure can be expected.

35 Schacht, F. W., and Crenshaw, J. L. Vesical Diverticulum in the Female, *J. Urol.* **24** 393 (Oct.) 1930.

36 Hamer, H. G. and Mertz, H. O. Angioma of the Bladder, *Surg. Gynec. Obst.* **51** 541 (Oct.) 1930.

PROSTATE GLAND

Hypertrophy—Cabot³⁷ stated that the most significant conditions leading to death following prostatectomy are renal insufficiency, bleeding, either primary or secondary, and infection. Satisfactory preoperative drainage is the best means of avoiding renal insufficiency. The control of primary hemorrhage or bleeding is satisfactory by either catheterization or suprapubic drainage. In primary prostatectomy the control may be carried out directly under sight, the bleeding points being secured by ligatures or sutures. This is a desirable procedure except that it may require considerable time and the prolongation of such operations may be inadvisable if the patients are elderly. In two-stage prostatectomy the control of bleeding, preferably by the use of a bag, but also by packing, has become entirely satisfactory and is probably as complete as that obtained by visual control. Neither method appears to have any advantage in secondary bleeding. This form of bleeding occasionally occurs after any method of prostatectomy, and does not appear to depend on the method employed. Following prostatectomy, infection may involve either the wound or the prevesical space or may occur in the region from which the prostate gland has been removed. In regard to infection of the wound and the prevesical space, the two-stage prostatectomy is a distinct advantage over the one-stage. If primary prostatectomy is carried out through an extensive incision allowing the operation to be done under direct vision there is more room for infection, more tissues are exposed and, since the operation necessarily is longer, there is greater strain on the resources of the patient and greater opportunity for infection. On the grounds of satisfactory drainage and liability to infection, the two-stage operation is better than the one-stage.

It has been widely believed that functional results following a one-stage prostatectomy carried out under direct vision were likely to be better than those following enucleation. Cabot observed more unsatisfactory results after the one-stage than after the two-stage operation, owing to contraction about the neck of the bladder, resulting in varying grades of stenosis, he expressed the belief that the former method has failed to show better results than the two-stage procedure.

The mortality of prostatectomy is relatively high and can be kept at its lowest level, from 2.5 to 5 per cent, only by taking every precaution. In the long run, the mortality of a properly carried out two-stage prostatectomy is apparently bound to be less than that following

37 Cabot, Hugh. The Place of Two-Stage Prostatectomy in Surgery of the Prostate Gland, Proc Staff Meet, Mayo Clin 5:247 (Sept 3) 1930.

the one-stage operation. The one-stage operation is more time-consuming and requires greater technical facility, more perfect surgical organization and superior judgment in the selection of cases. To secure the best results, it should be performed chiefly by the surgeons in whose hands perineal prostatectomy is now satisfactory, namely, the experts with large experience.

The requirements for a satisfactory two-stage operation are as follows. The first stage should be carried out in such a way as to avoid opening the prevesical space. The bladder should be opened and explored, the size of the prostate gland and the development of the various lobes should be noted, and the evidence of absence of calculi or diverticula should be confirmed. The drainage tube should be carefully placed in the bladder in such a way as to avoid contact with an enlarged median lobe. The wall of the bladder should be closed tightly about the tube to prevent leakage. The remainder of the wound should be carefully sutured and primary union should be obtained. If the operation is satisfactory, the patient is dry at all times, leakage around the drainage tube points to unsatisfactory technic. If it is possible to carry out the second stage within from seven to ten days, it should be possible to resuture the wound, although somewhat loosely, in such a way that rapid healing takes place, convalescence from the second stage of the operation should not be much longer than that following primary prostatectomy. Cabot concluded that two-stage prostatectomy is in general a safer procedure, that it will not prolong convalescence more than a week or ten days and that this time is well spent in obtaining a lower mortality.

Thomson-Walker³⁸ stated that the term "fibrous prostate" has crept into surgical nomenclature without careful definition of the type of its pathologic changes. From a series of 185 prostate glands in which full histologic details were obtained, he selected those weighing 20 Gm. or less as representative of glands of this type. After removal, a prostate gland of 18 or 20 Gm. does not appear larger than one would judge the normal gland to be. The author divided clinical forms of malignant growth of the prostate gland into two kinds, primary and secondary. In the primary malignant form, the change is, clinically at least, cancerous from the outset, in the secondary malignant form the gland has at first the character of the ordinary enlarged prostate gland and the malignant changes are engrafted on this. The proportion of primary to secondary malignant lesions of the prostate gland

³⁸ Thomson-Walker, John. Enlarged Prostate and Prostatectomy. II. Selection of Cases of Enlarged Prostate for Operation, *Lancet* 1:1219 (June 7) 1930.

is about 1.6. Of 2,496 cases of enlarged prostate gland observed by Thomson-Walker in private practice, the growth was malignant in 247 and a simple enlargement in 2,149. Thus the percentage of malignant growth was 13.5, and that of simple enlargement 86.5. The secondary malignant growth of the prostate gland is engrafted on simple enlargement of the gland. The malignant growth may develop in 1 of 3 situations, it may infiltrate the base of the prostate gland adjacent to the internal meatus and may not be discovered until operation is undertaken, the periphery of the enlarged gland may be affected. In these cases the examining finger recognizes an enlarged gland of elastic consistence. The third area to be affected is where the malignant change has developed in the substance of the enlarged prostate gland. The clinical features are those of simple enlargement of the gland, and at operation the enucleation proceeds smoothly. Attention was first drawn to this type of case by Albarran and Halle, who examined 100 specimens removed as simple enlargement of the prostate gland and found evidence of carcinoma in 14. In 521 cases in Thomson-Walker's private practice, a report obtained on the specimen removed by suprapubic prostatectomy revealed that there were 96 cases (18 per cent) in which areas of carcinoma were discovered. In these cases there was no suspicion of malignancy before operation, and the operation was performed by enucleation under the belief that the prostate gland was the seat of simple enlargement. It was stated that with increasing obstruction of an enlarged prostate gland and accumulation of residual urine, renal function is impaired, the renal insufficiency that results from urinary obstruction is that in which nitrogenous products are excreted in diminished quantity in the urine and accumulate in the blood.

Thomson-Walker concluded from the study of 274 cases that there is no risk of uremia following prostatectomy if the concentration of urea is 2 per cent or more, but that there is a slight risk when the reading is from 1.8 to 2 per cent, and that a single reading of 1.9 per cent is not sufficient to establish the case in this safe zone. There is serious risk when the figure is below 1.8 per cent, and more so when it is below 1.5 per cent. Furthermore, with extreme care it may be possible to operate successfully even when the concentration of urea is below 1.5 per cent. Estimation of the urea content of the blood gives additional information about the functional activity of the kidneys in the excretion of nitrogenous bodies. The normal urea content of the blood is from 20 to 40 mg per hundred cubic centimeters. MacLean pointed out that these figures are too low in dealing with older men, and that blood urea of from 40 to 50 mg per hundred cubic centimeters may be

present without indicating serious impairment of renal function. According to Thomson-Walker, sepsis in relation to the enlarged prostate gland and prostatectomy indicates failure of surgical methods. The infection may occur before the operation, it may be introduced at the time of operation or it may occur subsequent to the operation when the cystotomy wound is still open. If the infection is recent and moderate, and there is no evidence of renal involvement, a few weeks' preparation by thorough washing of the bladder and removal of the residual urine, either by intermittent catheterization or by use of the resident catheter, together with diuresis and urinary antiseptics, will suffice as a preparation for the removal of the prostate gland. When a more severe grade of sepsis is present, it will be necessary to perform suprapubic cystotomy and drain the bladder. A large proportion of the patients on whom prostatectomy is performed show signs of arteriosclerosis, a few have valvular disease and some have impairment of the myocardium. The degree of circulatory strain that is permissible in any given case will be decided by the physician and the anesthetist. Some of the patients run grave circulatory risks from the condition of the heart, as well as from the state of the blood pressure. The first point is that many patients submitted to prostatectomy have low blood pressures and a considerable number have very low pressures. Thus, of 107 consecutive patients, 44 (41.1 per cent) had a systolic pressure of 140 mm of mercury or less, and 19 (17.7 per cent) had a systolic pressure of 120 or less. With very high blood pressure one would expect serious hemorrhage, yet of 15 cases in which the systolic pressure was more than 200, severe postoperative hemorrhage occurred in only 2 (13.3 per cent), in none was the hemorrhage serious at operation. In low-grade pressures of 120 or less, more severe hemorrhage occurred in 4 cases (21.0 per cent) at operation, and in 2 cases (10.5 per cent) after operation. The lower the blood pressure the greater the probability of thrombosis and of pulmonary embolism. In 19 cases in which the blood pressure was 120 or less, there were 3 cases of thrombosis of pelvic or cerebral veins and 2 cases of pulmonary embolism (26.3 per cent), in the remaining 88 cases of the series there were only 2 (2.2 per cent) of thrombosis. In the entire series, only 1 patient died of sudden cardiac failure (systolic pressure, 200). Thomson-Walker's experience made him fear the danger of thrombosis and pulmonary embolism in cases in which the blood pressure is low. Of 16 patients with glycosuria on whom prostatectomy was performed, 12 (75 per cent) recovered from the operation and 4 died (25 per cent), diabetic coma was the cause of death of 2 patients within three days of the operation. Operation was performed on these patients before modern advances in the treatment of diabetes.

Thomson-Walker stated that the best form of treatment for the adenomatous prostate gland is removal by operation unless this is contraindicated. He believed that it has been the experience of all urologists that the operation can be successfully performed on extremely old men. Freyer related that in 1 625 cases of prostatectomy he had operated on 92 patients between the ages of 80 and 90 years, and on 13 in their eightieth year with 12 deaths (11.5 per cent). This is a fine record of work but the mortality here is twice that of his total average. In Thomson-Walker's own cases there were 27 patients aged 80 years or more, 3 patients died a death rate of 11.11 per cent, which closely corresponds to Freyer's figures. Constant skilled attention is necessary in these cases after operation. Another point in favor of early operation is the "silent" prostate gland with chronic urinary retention. This condition is one of the most difficult and dangerous in prostatic surgery. The only way to prevent the development of so grave a complication is thorough examination in all cases of frequent micturition and continued observation. If residual urine is found, operation should be recommended. Further reasons why operation should not be delayed indefinitely are the danger (1) of sepsis and (2) of malignant changes in a prostate gland which is the seat of simple enlargement.

Thomson-Walker stated that in the ordinary case, the two-stage operation does not appear to be safer than the one-stage operation. Shock is not a factor in uncomplicated one-stage prostatectomy. His experience has been that the second stage of a two-stage prostatectomy is much more likely to produce shock than a single-stage operation. If the open operation is performed when cystotomy has been done previously, it becomes necessary to dissect the whole of the scar tissue and to mobilize the bladder. The procedure is therefore much more serious than a single-stage operation. Hemorrhage is not less in a two-stage than in a one-stage operation. There was no question of sepsis being reduced in the cases commented on, for the bladder was aseptic. In the two-stage prostatectomy the bladder practically always becomes infected during the period of drainage before prostatectomy. Disadvantages of the two-stage operation are that there are two operations and two anesthetics, and the period during which the patient remains in bed is longer.

Gibson³⁹ stated that primary closure and healing are applicable to perineal prostatectomy wounds, and can be made the rule rather than the exception. Gauze packs or distensible rubber bags used for hemo-

³⁹ Gibson, T. E. Primary Closure in Prostatectomy. *Ann Surg* 92:82 (July) 1930.

static purposes are objectionable for a number of reasons. They stretch the dilated prostatic cavity still farther, which under ideal conditions should be permitted to collapse and shrink as soon as the gland is removed, they cause the patient discomfort, not only by their presence but by their removal, and they delay healing of the wound by leaving a temporary urinary fistula on withdrawal, which ordinarily requires from two to four weeks and perhaps longer to close.

Before primary closure can be done safely, it must be ascertained first that all bleeding has been carefully controlled. If bleeding can be satisfactorily controlled the wound is closed tightly without drainage, and the urinary stream is taken care of by means of a retention catheter through the urethra. If bleeding cannot be checked satisfactorily by suture the prostatic fossa is packed with strips of gauze.

In perineal prostatectomy it is generally possible to get an adequate view of the neck of the bladder, and in the majority of cases the wound can be closed without using either packs or bags. In a series of twenty consecutive operations for perineal prostatectomy, Gibson was able to do a primary closure successfully in thirteen. In the other seven he felt compelled to resort to packs to check the bleeding completely, thus making primary closure and primary healing impossible. Analyzing the two groups of cases with respect to duration of postoperative convalescence, the average time spent in the hospital by those for whom packs were used was twenty-two days. In the cases of primary closure in which packs were not used, the average time in the hospital after operation was sixteen days.

URETHRA

Calculi—Debenham⁴⁰ reviewed forty cases of urethral calculi recorded at the London Hospital during the last twenty years, impacted calculi occurred in thirty-four male and in three female patients. In the remaining three cases the condition was probably primary urethral calculi. In each instance there was a urethral stricture of long standing, and the symptoms suggested this condition combined with cystitis.

Urethral calculi are referred to as primary or secondary, according to their site of origin. Primary calculi are rare and are formed within the urethra either behind some obstruction or within the pouch. Secondary calculi are more common; they are formed in the kidney or bladder and are passed down the urethra. The most common site of the calculus is just proximal to the narrowest portions of the urethra. In the normal healthy urethra they are usually impacted either a short distance behind the external urinary meatus or in the prostatic portion.

⁴⁰ Debenham R. K. Urethral Calculi, *Brit J Urol* 2:113 (June) 1930.

of the urethra just behind the narrow membranous part. Primary and secondary calculi differ in their composition, a primary calculus is phosphatic, a secondary concretion is composed of any or all of the constituents that make up renal or vesical calculi. A primary stone may be dormant for a long time, the patient having symptoms suggesting urethral stricture or cystitis. The secondary calculus produces sudden obstruction either complete or partial, and necessitates immediate treatment.

In about half of the men the stone was impacted a short distance behind the urinary meatus. The calculi are usually small and single, rarely multiple, and vary in size from about 1.2 to 0.6 cm. In only one of the thirty-four cases of impacted calculi in men were the stones multiple. If the calculi are of the primary variety or if they have been lying for a long time in the urethra, for example, those found behind strictures, are more likely to be multiple and larger, as they no longer have to conform to the size of the normal urethra. Multiple stones are also often faceted. Large urethral calculi have not been noted, recently a case was reported of a Chinese boatman who had 2,170 stones weighing 81 Gm. in the urethra.

The symptoms produced by an impacted urethral calculus depend primarily on the extent of obstruction caused by the stone. When complete obstruction results, the typical history is that several hours previously, or perhaps the day before, the patient experiences sudden pain in the penis during urination, associated with sudden cessation in the flow of urine and occasionally followed by the passage of a few drops of blood. Retention of urine follows. When obstruction is partial, the history is often of longer duration, perhaps a day or two, or occasionally two weeks or more. In one case the calculus was impacted in the fossa navicularis of the urethra for twenty-three years. The calculus is often easily palpable in the urethra as a hard lump, especially if the stone is in the penile urethra. Sometimes, if near the external meatus, it may actually be visible. If situated in the prostatic urethra, it may be felt by rectal examination.

In most cases when the stone is situated in the anterior portion of the urethra, it can easily be recovered with forceps. If situated in the posterior urethra, the stone is pushed back into the bladder and then crushed. In some cases external urethrotomy is necessary, and incision is made over the stone, the stone removed and a catheter tied in the urethra for a few days. If the condition is complicated by a stricture of the urethra, dilation, or internal urethrotomy may be performed and forceps used to remove the stone.

Women rarely have urethral calculi as they do not often have vesical stones and as the urethra is short and dilates readily.

Caruncle —Olcott⁴¹ stated that the epithelium of caruncles of the female urethra frequently shows enough infolding to make the benign nature appear doubtful to one who is not familiar with this particular structure. Compound acinar glands similar to those described by Skene frequently are present in the female urethra. They were found in seventeen of the twenty-three cases considered. Olcott suggested that these glandular structures may be significant in the formation of caruncles. Twenty-three cases of caruncle were reviewed in which slides were satisfactory and the history fairly complete. The ages of the women varied from 23 to 55 years, the average age being 51. Of the fifteen patients whose marital status was recorded, ten were married and had borne children, three were married but childless, and two were unmarried. Complications noted were relaxation of the pelvic floor in six patients and probably in several others, hemorrhoids in two, diabetes in one and cystitis in one.

Hermaphroditism —Kleb's classification of true and false hermaphroditism and his subdivisions are generally accepted. For descriptive purposes the classification developed by Guenicoles into glandular and tubular hermaphroditism is most useful, the latter coming under the heading of false hermaphroditism.

McCrea⁴² reported a case of the tubular variety, that is, both Muller's and wolffian ducts were present in one person. This case is of additional interest as there was also a neoplasm of the internal genitalia. The patient, aged 31 years, was admitted to the male ward of the hospital in May, 1928 with the complaint of severe pain in the back, obstinate constipation and swelling of the abdomen which was rapidly increasing. Examination revealed a large abdominal tumor, apparently arising from the pelvis, which was about 20 cm. in size. The mass could be felt anteriorly by rectum. Neither testis was present in the scrotum. At operation a large, nodular tumor, partly cystic and partly solid was found, this rose from the pelvis and was adherent to the rectosigmoid. It was considered that the tumor was malignant, and probably arose from a retained testis. Operation was not possible. On searching for the testes both were found, but it was noted with some surprise that a tube with a fimbriated extremity lay in

41 Olcott, C. T. Urethral Caruncle in the Female. *Surg. Gynec. Obst.* 51: 61 (July) 1930.

42 McCrea, E. d'A. Tubular Hermaphrodite with Teratoma of the Internal Genitalia. *Brit. J. Surg.* 18: 91 (July) 1930.

relation to each. Complete exploration was impossible. Postmortem examination in July showed marked secondary involvement of the aortic glands and liver. Removal of the pelvic contents revealed a uterus with broad ligaments and tubes with fimbriated extremities passing to the two gonads previously noted, two vasa deferens passing down the posterolateral margins of the uterus in intimate relation with its wall, two seminal vesicles lying behind and to each side of the lower segment of the uterus, and a well developed prostate gland. The uterine cavity, which showed no evidence of division into uterus and vagina other than narrowing 2.5 cm from its inferior termination, opened into the prostatic urethra at the normal site of the prostatic utricle, and the length of its cavity from urethra to apex was 13.25 cm. The vasa deferens originated from two nodules lying between the layers of the broad ligament situated mesial to the two gonads, but clearly separate from them, they joined the ducts of the seminal vesicles, and the ejaculatory ducts opened at their normal sites on each side of the utricle. The tumor, 20 by 13 by 7 cm, appeared to be a teratoma, and had an attachment to the anterosuperior surface of the uterus and to the anterior aspect of the broad ligament. It had no relation to the two gonads or to the tubes, all of which were free and clearly demonstrated at the operation in May, although at necropsy the appendages of the left side were partially obscured by the tumor and its secondary growths. Microscopic examination revealed that the uterus possessed an apparently normal endometrium and a wall made up of smooth muscle, the tubes, seminal vesicles, vas deferens and prostate gland appeared normal. The gonad of the right side was definitely a testis, and serial section failed to show any trace of ovarian tissue, the left gonad, which was largely destroyed by secondary growths, also proved to be a testis. The tumor contained numerous cysts, the majority of which showed intracystic papillomas, among other tissues found were bone, cartilage, smooth muscle and tubules lined with epithelium. Ectodermal derivatives identified were some rudimentary teeth and a small cyst lined by squamous epithelium from which a few hairs sprang. All the secondary growths examined were papilliferous cystadenomas. It was noted that the patient was typically masculine, without any evidence of female characteristics. A history obtained from his brother and roommate however disclosed that since the age of 17 there had been attacks of abdominal pain "nearly every month, periodical like a woman," and at such times it was observed that the urine was stained with blood.

UROGRAPHY

Jona and Flecker⁴³ stated that pyeloscopy is a convenient method for determining the pathologic changes in cases of pain in the kidney when lithiasis is absent. In many cases of pyelitis these investigators have determined by direct observation which drug gives the best contraction of the renal pelvis. Patients who have suffered for years from backache with periodic exacerbations of headache, sweating and rise of temperature, have derived immediate relief from strychnine, physostigmine and morphine, either alone or combined, when citrates and the usually recognized treatments have failed. In cases of hydronephrosis in which the pelvis contracts well and vigorously, the treatment is plication, if the pelvis does not contract and is simply an inert atonic sac nephrectomy is indicated. In cases in which a malignant lesion occurs early, involving perhaps only a single calix, the absence of contraction of one part of the pelvis associated with "idiopathic" hematuria of renal origin would justify an exploratory operation. In the opinion of Jona and Flecker, too much stress cannot be laid on the necessity for slow injection into the pelvis of the kidney and the danger of rupture occurring if nature's warning of pain is ignored.

Iopax.—Braasch⁴⁴ stated that from the experience of those who have employed iopax its greatest value probably will be in determining the condition of the kidneys in cases in which ureteral catheterization is difficult or impossible. This would include cases of intolerance, a contracted and tuberculous bladder, anatomic obstruction of the ureter, extensive vesical neoplasm, prostatic obstruction, impassable stricture of the urethra, ectal implantation of the uterus and, in infants and older patients, cases in which introduction of the cystoscope is difficult because of deformities. The intravenous method permits bilateral pyelography without the dangers accompanying bilateral retrograde pyelography, this should be of particular value in the presence of polycystic kidney, bilateral hydronephrosis and fused and solitary kidney. It will also be helpful to the lists of tests of differential renal function, which frequently have left doubt as to the functional capacity of the kidney under investigation. Iopax offers a better medium for retrograde pyelograms than sodium iodide, since it has none of the irritating qualities of the latter and since because of the large content of iodine, it casts a dense shadow.

43 Jona J. L., and Flecker H. Pyeloscopy. Radioscopy of the Kidney Pelvis. *Surg. Gynec. Obst.* 51: 50 (July) 1930.

44 Braasch W. F. Intravenous Urography, editorial. *Surg. Gynec. Obst.* 51: 421 (Sept.) 1930.

Although the method of intravenous urography is available to the general practitioner, interpretation of the urogram frequently is difficult and should be referred to those who have had extensive experience. In some cases the use of iopax may render cystoscopic examination unnecessary, but its interpretation will often have to be accompanied by cystoscopic data in order to complete the diagnosis.

Galbraith and Mackey⁴⁵ stated that iopax contains 42 per cent of iodine by weight and is possessed of a high degree of radiopacity. The original clinical investigations were carried out by von Lichtenberg and Swick. This drug, injected intravenously in solution, is rapidly excreted by the kidneys almost in its entirety. Roentgenograms taken during excretion of the drug give satisfactory visualization of the urinary tract. In a preliminary series of experiments on animals with iopax, Galbraith and Mackey's object was to determine whether or not this drug was capable of injuring the renal parenchyma. For this purpose they employed rabbits and administered the standard dose for man for each kilogram of body weight, and a series of larger doses up to seven and a half times the standard amount. Fairly satisfactory visualization of the urinary tract was obtained by the standard dose, and it is noteworthy that improvement in the roentgenographic pictures did not follow the use of larger doses. It is Galbraith's and Mackey's belief that the sharp demonstration of the renal parenchyma may prove a valuable feature of the method in human beings. A toxic effect was not produced in any animal even with the larger doses. Microscopic examination of the kidneys failed to reveal evidence of injury to the renal parenchyma, either immediately after the excretion of iopax or at intervals up to forty days after treatment.

Galbraith and Mackey concluded that iopax is practically harmless and is unlikely to produce injury when used in doses sufficient to give satisfactory roentgenographic pictures.

Urethrography—Knutsson⁴⁶ after briefly reviewing the method used in urography, described a clamp for the penis made for that particular purpose. The clamp makes the examination simpler and more convenient. He also commented on the so-called collicular elongation of the posterior urethra. In contradiction with Dressler he holds that only from 1 to 2 cm. of the shadow above the colliculus seminalis is caused by the urethra and that the remaining part of it is caused by some of the opaque fluid collecting in a fold of mucous membrane at the bottom of

45 Galbraith, W. W., and Mackey, W. A. Uroselectan. A Preliminary Experimental Note. *Brit. J. Urol.* 2:122 (June) 1930.

46 Knutsson, Folke. On the Technique of Urethrography, *Acta radiol.* 10:437, 1929.

the bladder. The elongation of the urethra is thus only apparent, and it is not of significance in estimating the size of the prostate gland.

INFECTION OF THE URINARY TRACT

Von Lichtenberg⁴⁷ considered the juncture of the urinary and genital tracts a potential source for the spread of disease. The intimate topographic contact with a common blood, lymph and nerve supply makes it seem inevitable that a pathologic process in one of the tracts will also affect the other. A primary, exogenous infection of the prostate gland and seminal vesicles will be the etiologic factor for secondary pathologic changes in the upper part of the urinary tract. A number of cases of ureteral stricture, ureteral kinks, periureteritis, perinephritis and pyogenic renal disease are caused by diseases of the adnexa.

A point of view of pathologic change in the system leads to a correct diagnosis in such cases and forms the background for proper treatment. It allows the correct pathologic evaluation of ureteral disease. By this means von Lichtenberg found the connecting link which joins the diseases of the lower urinary tract and genital organs with those of the kidney into one pathologic and clinical unit.

Von Lichtenberg divided the cases into two large groups: those in which cure can be effected by conservative treatment of the adnexa, and those in which a surgical procedure is necessary to produce healing. Except in cases in which the disease of the vesical sphincter is already the cause of residual urine, operation is performed only after conservative treatment has been unsuccessful.

Conservative treatment consists of diathermy of the adnexa, injections of sulphonated bitumen, N. F. sitz-baths and intravenous injections of sodium iodide, acriflavine, mercurochrome-220 soluble, arsphenamine and methenamine. Von Lichtenberg has seen good results after the long-continued use of hexylresorcinol with diathermy. It seems to have a favorable influence on postgonorrheal infections of the adnexa.

[ED. NOTE.—It is remarkable that in the past so little emphasis was placed on the causal relationship between genito-urinary and adnexal diseases. Recent American literature on the subject is especially scanty. Urologists in this country have, as pointed out by Braasch, paid more attention to distant foci of infection. For this reason, von Lichtenberg's article presents a point of view that will doubtless arouse much interest and comment. Hunner has often emphasized the relationship of endocervicitis, adnexal inflammation and even normal pregnancy to the

⁴⁷ von Lichtenberg, A. Kidney and Ureteral Lesions Secondary to Adnexal Disease, *J. Urol.* **24**: 1 (July) 1930.

development of ureteral stricture and stasis of the urinary tract Von Lichtenberg, while avoiding this subject, brings out ideas of the same general order The urologist must study his male patients carefully from the standpoint of related prostatic or seminal vesical disease, in a study of women the intimate cooperation of the gynecologist must be sought if the urologist is not also a gynecologist Operative measures are to be reserved for those cases which do not respond to more conservative types of treatment such as outlined by von Lichtenberg]

Keyes ⁴⁸ stated that because genital infections are often old and almost forgotten by the patient, they are easily overlooked when urinary trouble arises Contact of the seminal vesicle with the ureter is of great interest in cases of ureteral stricture and renal infection

Braasch ⁴⁹ observed that, in looking for foci of infection with chronic urinary infections American urologists have paid more attention to tonsils and to teeth than to the adnexa Many have recognized these adnexal infections and treated them, as well as other foci, by both conservative and radical methods, without reducing the degree of infection in the kidneys Von Lichtenberg has not only removed foci, but has attempted to overcome any possible interference in renal drainage He frees the ureter from both periureteral and intra-ureteral obstructions He also frees the kidney from adhesions and performs nephropexy, believing that the renal position or para renal obstructions may interfere with urinary drainage He drains the kidney by putting a catheter through the cortex by his own method

In reviewing 1,200 cases of chronic infections of the kidney, Braasch found that nature aids in remedying these conditions Of the various methods employed, no single procedure could be regarded as a panacea At the end of five years a third of the patients were free from symptoms, apparently largely spontaneously, although they had undergone every form of treatment A considerable percentage of the remaining two-thirds should be benefited by the treatment outlined by von Lichtenberg One of the urologic problems that remains to be solved is the discovery of some method, either by vaccine or intravenous medication, to overcome chronic infections in the kidney which do not respond to various forms of treatment now employed

In women, chronic pyelonephritis occurs in less than 40 per cent, whereas acute pyelonephritis occurs in approximately 80 per cent A careful search should be made for pelvic infection, and, if present, it should be removed The cervix should be examined carefully as a possible

48 Keyes, E. L., in discussion of von Lichtenberg (footnote 47)

49 Braasch W. F., in discussion of von Lichtenberg (footnote 47)

focus of infection and cultures are frequently indicated. In many cases, amputation of the cervix was indicated, and in some cases this procedure was followed by excellent results.

Oeconomos⁵⁰ stated that infection of the urinary tract by colon bacillus is of significance because of its frequency, manifold clinical forms, complications, sometimes difficult diagnosis and the numerous and new treatments. In certain circumstances toxins are secreted, the intestinal epithelium is altered, and the colon bacillus enters the blood, it may determine septicemia, in the course of which the organism can be localized as a result of urinary stasis in the kidneys, ureters, bladder, prostate gland, seminal vesicles and urethra, thus manifesting the complete range of the urinary infections.

The origin of such a condition is often an infection of the intestines especially fecal stasis and the presence of intestinal parasites. Fecal stasis brings about erosions or intestinal changes that allow the colon bacillus to filter through the intestinal walls, producing autointoxication. Urinary stasis is the prime factor in localizing this infection through the urinary organs. From the experimental point of view, the colon bacillus acts by means of its toxins, which are more dangerous as they become older. This bacillus often follows the hematogenous route through two stages, it first enters the lymphatic vessels and finally pours into the general circulation.

The treatment of infection of the urinary tract by the colon bacillus must be directed to stasis, the infection, and the initial lesion giving rise to the infection. Stasis should be controlled by the proper methods and the infection by the serum anticolon bacillus of Vincent. If stasis is not apparent treatment should be directed toward the intestines by diet, administration of liquid petrolatum, lavage, etc. with regard to the urinary tract collargol should be given by mouth alternating with phenyl salicylate, associated with methylene blue (methylthionine chloride U. S. P.) and the tract should be lavaged. The infection should be attacked by the anti-*Bacillus coli* serum of Vincent.

Bacteriophagy—Krueger, Faber and Schultz⁵¹ stated that data obtained by periodic examinations of specimens of urine from eight cases of acute urinary infection in which alkalis were given by mouth indicate that alkalization, when effective, may facilitate an increase of the virulence of bacteriophages naturally occurring in the urine, probably by providing the optimal reaction for bacteriophagy. In twelve cases of acute

⁵⁰ Oeconomos Spyridion. *Bacillus Coli* Infection of the Urinary Apparatus. *Brit J Urol* **2** 141 (June) 1930.

⁵¹ Krueger A. P., Faber H. K. and Schultz E. W. Observations on the Bacteriophage in Infections of the Urinary Tract. *J Urol* **23** 397 (April) 1930.

infection of the urinary tract, a strain of colon bacillus resistant to the bacteriophages was harbored in one (8 per cent), whereas in seventy-seven cases of chronic infection of the urinary tract, forty-two patients (54 per cent) were infected with organisms resistant to bacteriophages. In thirty-five cases of chronic conditions, bacteria were harbored that were capable of complete lysis by one or more races of bacteriophages. In only three of sixteen cases in which pooled suspensions were given was prompt recovery noted, two patients failed to respond to the treatment, and eleven gradually recovered. Of nineteen patients to whom matched individual races of bacteriophages were administered, only one recovered promptly, four failed to recover and fourteen recovered gradually. Twenty-five of thirty-five patients recovered gradually, their recovery was not definitely attributable to the bacteriophages. Four patients recovered rapidly and six failed to recover.

The general trend of the results does not make it possible to state with accuracy how much value may be attributable to the bacteriophage as a therapeutic agent in chronic urinary infection. The limited number of cases would preclude any far-reaching conclusions. In the experience of these investigators the bacteriophage treatment for urinary infection has failed to realize the good results reported by previous investigators.

Martin⁵² expressed the opinion that to obtain restoration to normal of diseased urinary organs, it is necessary to reestablish the free flow of urine to eradicate the origin of disease, to collaborate with nature and to seek the help of an antiseptic if there is one for the germ in question.

Jaeggy⁵³ emphasized the necessity of taking into account the manner of urinary infections and at the same time of treating the primary source, if possible. The true urinary acidity should be found and controlled daily during treatment. A simple and rapid method of determining the true urinary acidity was described. For practical purposes it is well to distinguish strong or weak alkalinity, and strong, medium or weak acidity. From the evidence of numerous works on the subject the value of urinary antiseptics hardly agrees with their bacteriologic power *in vitro*. The greater part of such preparations react sooner in a medium as stimulants to means of defense rather than as bactericides. The old preparations of phenyl salicylate, methenamine, camphoric acid and the balsams continue to retain the positions acquired, and have hardly been supplanted by new preparations. Among the latter, the arsenobenzols, owing to their almost specific action

52 Martin A P. Urinary Antiseptics. *Brit J Urol* 2:139 (June) 1930.

53 Jaeggy E. Urinary Antiseptics. *Brit J Urol* 2:140 (June) 1930.

against staphylococci, have shown value as a therapeutic measure. Mercuriochrome-220 soluble should be reserved for conditions that have resisted milder remedies.

CHYLURIA

Kidd⁵⁴ described two cases of chyluria and filariasis in which surgical treatment was given. One patient who had been treated for infection of the urinary tract later passed large quantities of milklike urine. A catheterized specimen looked like milk, and microscopically it contained large numbers of minute fat droplets, there were traces of pus and bacilli. Specimens taken from the right kidney on two separate occasions contained fat, the urine from the left kidney was normal. A roentgenogram was negative for stone, but pyelograms showed a dilated hydronephrotic right kidney. Filarial embryos could not be found in the blood or the urine. Abdominal nephrectomy was performed. The rectus muscle was turned inward, and the peritoneal cavity was opened and explored, evidences of dilated abdominal lymphatic glands, however, could not be detected. The right kidney was exposed by cutting the peritoneum outside the ascending colon. The right ureter at the ureteropelvic junction formed an S-shaped kink with high valvular insertion of the ureters into the pelvis. The pelvis appeared as a distended cyst, and the renal substance was lobulated and thinned to less than a third of its usual thickness. The blood supply was normal. The kidney was hardened in formaldehyde and then opened and dissected. Evidence of the presence of filarial worms or embryos could not be found. The appearance was that of infection and hydronephrosis. Convalescence was uneventful.

In a number of cases of chyluria reported in recent years, ureteral catheterization showed that the disease was confined to one kidney. In many cases the symptoms were not severe enough to warrant operative procedure, only six are reported in the literature in which operation was performed, and in only three cases was it successful. Kidd found it necessary to operate in the first case on account of the presence of congenital hydronephrosis. In the second case, that of a youth, aged 19, the left testis was greatly enlarged, pear-shaped, elastic and tense, it could not be determined whether the swelling was fluid or solid. An exploratory operation was performed, the testis being exposed through a long incision extending from over the cord, the full length of the scrotum. The tunica vaginalis, tensely distended with nontranslucent fluid, was incised and a large quantity of fluid resembling milk

⁵⁴ Kidd Frank. Surgical Treatment of Chyluria and Filariasis, *Brit J Urol* 2: 15 (March) 1930.

escaped. Examination of the cord revealed a number of tortuous dilated lymph vessels filled with clear translucent fluid. The majority of these lymphatic glands were cut across, allowing the fluid to escape. On further examination the fluid was found to contain embryos of *Filaria sanguinis-hominis* in an active state but no trace of fat. The hydrocele sac was removed, and the major portion of the skin was stitched up, provision being made for adequate drainage of the fluid. Recovery was uneventful. Fluid continued to escape from the wound for about three weeks, after which the wound became dry and healed soundly. The left testis, when examined eight months later, appeared to be normal. This case suggests the following surgical principle in dealing with filariasis. When an exposed organ is found to present a large number of varicose lymphatic glands distended with clear, milky or pink fluid, the condition is probably due to filariasis, and it may be worth while to cut across the main mass of dilated lymphatic glands and arrange for suitable drainage to the surface of the skin.

From a review of the literature the prognosis of chyluria seems to be unfavorable. In the presence of renal or vesical colic, large doses of sodium citrate prevent coagulation of the fibrin, with relief of the symptoms. Secondary infections of the kidneys and bladder should be treated by renal and vesical lavage and by urinary antiseptics. Aisphenamine or neoarsphenamine may sometimes exert a lethal effect on the parasites, and should be tried in all cases before surgical intervention. Intravenous injections of tartar emetic have also produced good results, and may be tried if aisphenamine fails. Kidd expressed the belief that if chyluria is unilateral, if drugs fail to cure it and if the patient is losing weight or suffering from painful symptoms, nephrectomy is apparently justifiable and may bring about a cure. In cases of bilateral renal chyluria, if there are dangerous complications, exposure of each kidney and upper end of the ureter from behind the peritoneum by two separate incisions, with incision of the lymph varices if found and provision for their drainage to the skin, may prove beneficial. A successful surgical attack has been made on vesical chyluria. Bloch in 1913, cured such a condition by destroying with the cautery snare a burst lymph varix which he could see in the wall of the bladder.

DYSFUNCTION OF THE NERVE

Mertz and Smith⁵⁵ reviewed thirty-nine cases of dysfunction of the nerves of the urinary tract, thirteen of which were their own. In

⁵⁵ Mertz, H. O., and Smith, L. A. Posterior Spinal Fusion Defects and Nerve Dysfunction of the Urinary Tract, *J. Urol.* **24**: 41 (July) 1930.

six of the twenty-six cases reviewed from the literature, observations made at necropsy were given. In thirty-four cases the complaint was urinary incontinence, associated with retention of urine in fifteen. Retention of urine without incontinence occurred in three cases. In eleven cases the retention was associated with urinary reflux and dilated ureters and pelvis, while in one case there was retention of badly infected urine without urinary reflux or ureteral changes. Coexisting neurotrophic changes involved the renal sphincter in eleven cases, and the lower extremities in eleven cases. Disturbed sensation of the legs or about the vulva or anus was noted in four cases. Unusual conditions of the skin over the lumbosacral region, such as hypertrichosis, discoloration, tumor, dimpling and postoperative scar, were present in eight cases. In two cases, no evidence of paresthesia or trophic changes in the extremities was found at operation. Operation was performed in twenty-one cases reviewed from the literature, in two cases which Meitz and Smith had observed, operation benefited one patient and cured the other. Observations at operation and the clinical results following operation indicated nerve dysfunction. Roentgenograms of the lumbosacral region in thirty-three cases showed varying degrees of anomaly of spinal fusion. In nine cases injection of iodized poppy seed oil 40 per cent was made into the subarachnoid space, seven cases showed definite evidences of local pressure on the nerve structures, in one case the observations were indefinite and in one they were misleading.

INTRAPERITONEAL PRESSURE^{*}

RICHARD H. OVERHOLT, M.D.

PHILADELPHIA

Pressure conditions which exist within the peritoneal cavity have received much less attention than that given to considerations of the pressure within other body cavities. Since one understands pressure to be the action of a force against an opposing force, it is possible to think of a pressure within the cleft between the parietal and the opposing visceral peritoneum.

Under normal conditions the peritoneal cavity, as it is known anatomically, is not a cavity but a cleft. However, in this discussion the term peritoneal cavity will, because of its wider usage, be used to denote the potential peritoneal space, or, more strictly speaking, the peritoneal cleft. The ramifications of this cleft extend, for the most part, throughout the abdominal cavity and between the various organs. Nothing is contained within this space except a small amount of peritoneal fluid which moistens its surfaces. There is no communication with the outside except through the fallopian tubes in the female, and this communication is of no practical importance so far as pressures are concerned. The reflections of the parietal peritoneum conform, for the most part, to the limitations of the abdominal cavity. Since practically all of the remainder of the peritoneum covers the viscera and moves about within the parietal peritoneum, the consideration of pressure values between these components of the peritoneum are, for all practical purposes, considerations of pressure values within the so-called abdominal cavity.

Mechanically, the abdomen has been considered by Krause,¹ Hitzengerber² and Wildegas³ as a closed box with partially rigid and partially flexible walls, so that pressure values would follow hydrostatic laws for such containers. The degree of flexibility of the walls and the specific gravity of the contents would determine the pressure at any given point. With a portion of the container rigid (spine) and an anchorage above

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¹ Krause, N. J. Der intraabdominelle Druck im Bereiche Epigastriums und dessen Bedeutung in der Magen Chirurgie, *Arch f klin Chir* **144** 201, 1927.

² Hitzengerber, K. Zwerchfall und Intraperitoneal Druck, *Klin Wchnschr* **8** 961 (May) 1929.

³ Wildegas, H. Ueber den intraperitonealen Druck, *Mitt a d Grenzgeb d Med u Chir* **37** 308 1923.

(costal arch), there is a tendency for the container to maintain its shape in various positions. The weight of the contents causes a bulging in the dependent portions and a sinking in the upper portions (fig 1)

Simple mechanical explanations of pressure alterations in the abdominal cavity are complicated by a movable partition above (the diaphragm), by attachments to a shifting costal arch, by living contractile abdominal walls and by contained viscera some of which may be full or empty and may contain gas collections, fluid or solid matter.

There has been considerable speculation as to the pressure conditions that exist within the peritoneal cavity. Many investigators have reported work on intra-abdominal pressure by recording volume changes in balloons inserted in the rectum, stomach or bladder. This determined intra-intestinal or intravesicular pressure and not intraperitoneal pressure. According to Keppich,⁴ Winkler was the first to measure pressures in the peritoneal cavity by inserting a trocar and connecting it with a water manometer. In a similar way, many other investigators have measured the intraperitoneal pressure. There has been consider-

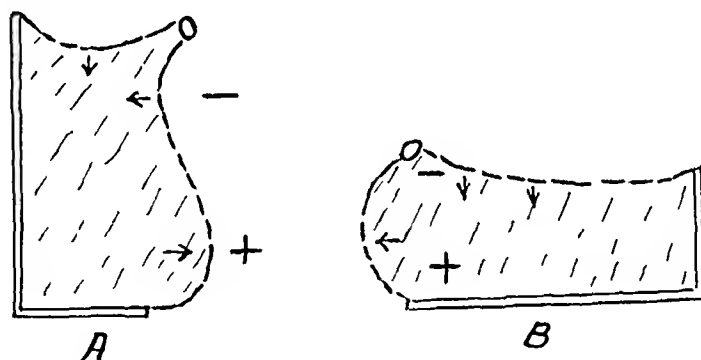


Fig 1—Diagram of an airtight container with partially rigid and partially distensible walls filled with fluid (After Krause). The effects of gravitation on pressure exerted at various points are shown, A, erect position, B, horizontal position. The anchorage of the flexible walls above corresponds in the diagram to the part the spine and costal arch play in the upper part of the abdomen.

able disagreement as to whether it is above or below atmospheric pressure. Kelling,⁵ Hormann⁶ and others thought it necessary to inject air or water before the pressure could be measured. Such injections in themselves alter the existing pressure. Likewise, all observations on patients with ascites at the time of an abdominal paracentesis do not represent the true pressure. Quirin⁷ and others first opened the peri-

4 Keppich, J. Intraperitoneal Druck, *Arch f klin Chir* **116** 276, 1921.

5 Kelling, G. Quoted by Keppich, footnote 4.

6 Hormann, K. Quoted by Emerson, footnote 8.

7 Quirin, A. Ueber das Verhalten des normalen und pathologisch gesteigerten intraabdominalen Druckes und seine Rückwirkung auf die arterielle Blut-circulation, *Deutsches Arch f klin Med* **71** 79, 1901.

toneal cavity and then sutured a cannula in place. This method is also open to the same objection.

In 1911, Emerson⁸ made an exhaustive review of the literature on this subject, and concluded that the majority of investigators had found a pressure in the peritoneal cavity which exceeded atmospheric pressure. During his own experiments on rabbits and dogs, he made similar observations.

More recently, Wildegras³ has contended that the intraperitoneal pressure is as a rule slightly greater than atmospheric pressure. Keppich,⁴ Melchior and Melchior,⁹ Wagoner¹⁰ and others have consistently recorded subatmospheric pressures by using a large bore needle cannula and a water manometer.

Practically all investigators have reported shifts in the intraperitoneal pressures with the phases of respiration, as evidenced by an inspiratory increase (diaphragmatic contraction) and an expiratory decrease (diaphragmatic relaxation) in pressure. Keppich⁴ was unable to record these variations, and he also pointed out that it was impossible to influence the intraperitoneal pressure by straining, by pressure on the chest or by shifting the position of the animal.

Much of the confusion is undoubtedly due to two things. 1. Most investigators have taken pressure readings at only one point in the abdomen. 2. All have used a needle or cannula connected with a water manometer. Whenever the open U-tube water manometer is used to measure pressures, the shift of the column of water in the manometer produces a corresponding displacement of air in the connecting tube and cannula. If the pressure is below atmospheric pressure, a certain amount of air is lost from the measuring system and passes into the abdomen. If the intraperitoneal pressure exceeds atmospheric pressure, the displacement required to effect a shift of the manometer causes the visceral peritoneum to seal the openings in the cannula, and a true pressure cannot be registered. It is probably because of this difficulty in measuring pressures greater than atmospheric pressure that many investigators record readings only in the epigastrium, where the pressure is usually subatmospheric. Wagoner¹⁰ evidently had the same trouble, for he says: "No intra-abdominal pressure readings are obtainable with the animal in this position (horizontal) if the needle be inserted posteriorly or posterolaterally, due to the posterior gravitation of the abdominal viscera."

⁸ Emerson, H. Intra-abdominal Pressures, *Arch Int Med* 7:754, 1911.

⁹ Melchior, E., and Melchior, P. Intraperitoneal Druck, *Arch f klin Chr* 119:148, 1922.

¹⁰ Wagoner, G. W. Studies on Intra-abdominal Pressure, *Am J M Sc* 171:697 (May) 1926.

METHOD

Dogs were used in all of these experiments. In most instances, the animals were anesthetized with one of the barbital derivatives, 50 mg per kilogram of body weight being administered. The barbital derivative was administered intravenously in some and intraperitoneally in others. No differences in the results were observed as a consequence of the method of administering the anesthetic. Observations were also made on trained, unanesthetized dogs, the cannula being inserted after the local infiltration of procaine hydrochloride. Animals were also observed immediately after death.

An adjustable table was used so that the position of the dog could be changed without effecting the recording apparatus. The animal could be fastened to this table and tilted head up or head down or rotated on the horizontal axis so that the anterior abdominal wall was above, on the side or dependent.

A right-angled cannula was devised which could be inserted through a small incision in the skin, and pushed into the peritoneal cavity without the possibility

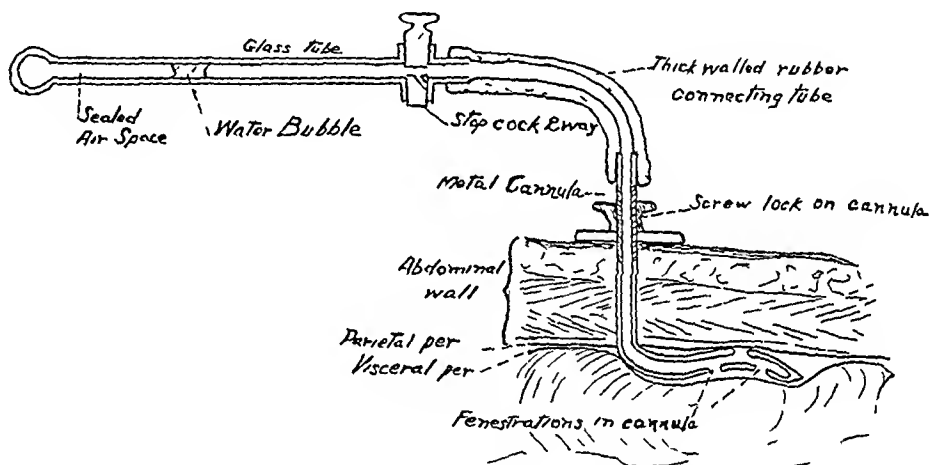


Fig 2—Diagram of the apparatus used in measuring intraperitoneal pressure. The variations of pressure within the cannula cause a fluctuation of the water bubble in the closed manometer, which was designed by Lewis. The instrument was calibrated against a water manometer and the linear displacement of the water bubble noted under a microscope or projected on a movable photographic screen. A water bath is constructed about the manometer. This is not shown in the diagram.

of the entrance of air. The cannula was made with a solid tip and several side openings, so that occlusion of the lumen would not take place. A thumb screw and washer were placed on the shaft so that the cannula could be held securely in place without the possibility of shifting or leakage (fig 2). The cannula was introduced in different locations of the abdomen. For measuring the pressure in the upper portion of the peritoneal cleft, the cannula was inserted in the epigastrium either to the right or the left of the midline. For the pressure in the lower peritoneal cleft, the cannula was inserted in the right or left lower quadrant. In determining the pressure in the posterior portion of the peritoneal cleft, the right or left costovertebral angle was used as the point of entrance for the cannula.

For recording the pressure changes various methods were used. In the first animals studied, a water manometer was connected directly to the cannula before it was inserted. In some, a tambour was connected, and tracings were made on a smoked drum. The objections to the direct measurement of the pressure by the U-tube manometer were overcome by the use of a closed system manometer devised by Lewis¹¹. This instrument consists of a hollow glass tube sealed at one end, a water bubble in the shaft of the tube and a two-way stop-cock at the opposite end (fig 2). With this tube connected to the cannula in the abdomen, variations in pressure cause a shift of the bubble. The movement of the bubble is, however, reduced because of the sealed end of the glass tube, its amplitude for any given pressure being determined by the volume of the air in the sealed space. The exact linear displacement of the bubble was so small that it was necessary to take the measurements with microscopic magnification. The portion of the water bubble at atmospheric pressure was determined by opening the stop-cock and at the same time closing off that part of the system which was in communication with the peritoneal cavity. A water bath constructed about the manometer prevented any changes in volume as a result of temperature variations. Photographic records of the movement of the bubble of water were made by projecting a beam of light through the microscope and focusing it on a moving film. For this the recording part of an electrocardiograph was used. Each closed manometer tube was carefully calibrated against a water manometer and by actual calculation. Such a method met most of the objections of the open system. The volume shift at the end of the cannula was estimated to be less than 3 or 4 mm, so that positive pressures could be measured without the valvelike occlusion of the cannula openings by the visceral peritoneum. Capillarity of the water column in the manometer was avoided. The factor of inertia of the water column in the U-tube manometer was eliminated.

Various procedures were carried out for the purpose of altering the pressure within the peritoneal cavity. Moderate pressure of the hand on the abdomen and the application of a muslin binder were used to alter the flexibility of the anterior abdominal wall. The stomach and colon were distended by inflating balloons after their insertion.

Known amounts of air were injected into the abdomen to study the effects of pneumoperitoneum on the intraperitoneal pressure. One animal was eviscerated, the abdominal cavity filled with water, and the abdominal wall closed. In this animal pressure observations were made with the same apparatus that was used in the living animal¹².

RESULTS

Animal on Its Back in Horizontal Position—With the cannula in the epigastrium readings were made on thirty-three animals. A mean subatmospheric pressure was recorded in thirty-two of the animals. This mean is the value between inspiration and expiration. The values

¹¹ Lewis, R. M. A Closed System Manometer, to be published.

¹² At the suggestion of Prof. H. C. Bazett, of the Department of Physiology, one observation was made on the intraperitoneal pressure after the insertion of a cannula in the epigastrium with the dog in the horizontal position. A method of mirror reflexion was used, and subatmospheric pressures were demonstrated.

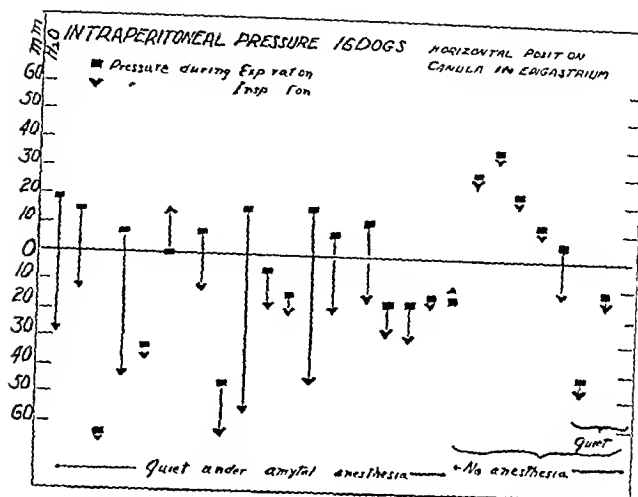


Fig 3—Graph showing intraperitoneal pressure values obtained in sixteen animals. The cannula was in the epigastrium and the animals placed on their backs in the horizontal position. The extremes of the arrows show the actual pressure variation during the two phases of respiration. Note that the majority of the readings were below atmospheric pressure, and that the pressure fell during inspiration in all but two instances.

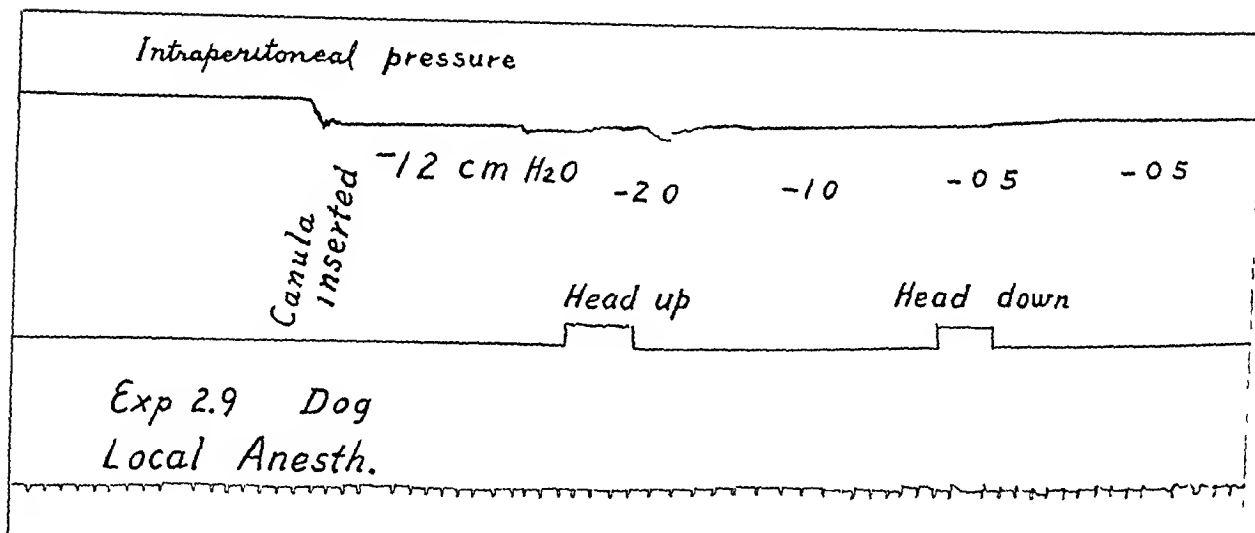


Fig 4 (dog 203)—Weight of animal, 19 Kg. Kymographic tracing showing curve of the intraperitoneal pressure with animal on its back in a horizontal position. Local anesthesia was used. Note the drop in the pressure from the atmospheric level as cannula was inserted and the absence of marked changes in pressure with alterations of position due to the lack of anesthesia. Note the absence of respiratory excursions in this record. The readings were recorded in centimeters of water pressure.

varied from 5 to 100 mm of water pressure. In one animal the pressure was zero (fig 3). Subatmospheric pressures were also obtained in two dead animals. In three animals in which no anesthesia was given, the intraperitoneal pressure in the epigastrium was below the atmospheric value in two and above in one (fig 4).

No relationship could be worked out between the weight of the animals and the pressure found in the peritoneal cavities of the animals in the horizontal position. Pressures were found to be lowest when the animal was deeply anesthetized. Under such conditions, the pressure became even still lower if the legs of the animal were stretched so that the concavity of the anterior abdominal wall approached a straight line. If the animal was lightly anesthetized or was straining, the pressure became greater, and its rise was even more marked when the legs were stretched, that is, the pressure values were reversed.

Relation of Respiration to Intraperitoneal Pressure—In the experiments in which the U-tube manometer was used, we were unable normally to detect fluctuations in the intraperitoneal pressures caused by the respiratory excursions. Following the injection of a small amount (from 2 to 5 cc) of air into the peritoneal cavity at the site of the cannula, respiratory excursions could be recorded.

However, we were able to observe in the normal animal variations in pressure with the respiratory phases without the induction of a pneumoperitoneum by using the closed water bubble manometer devised by Lewis (figs 5, 6 and 7). In seventeen animals that were breathing quietly and regularly it was found that the pressure in the peritoneal cavity decreased during inspiration and increased during expiration. This is contrary to the results obtained by other observers.

The same inspiratory decrease in the intraperitoneal pressure was noted when the cannula was inserted in the lower part of the abdomen or in the costovertebral angle. The same observation was made in the animals that had only local anesthesia for the insertion of the needles. In fact, a change in the position of the animals did not alter this relation of pressure variation to the respiratory phase so long as the quiet, even type of breathing was undisturbed.

However, if the animal strained under light anesthesia, struggled under no anesthesia, or had an irregular abdominal type of breathing the pressure variations within the peritoneal cavity were reversed. The increase was noted during inspiration (diaphragmatic descent) and was decreased during expiration (diaphragmatic relaxation).

Relative Positions of the Cannula and the Animal—With the cannula in the lower part of the abdomen and the animal placed in the horizontal position, the mean pressure in the majority of instances was

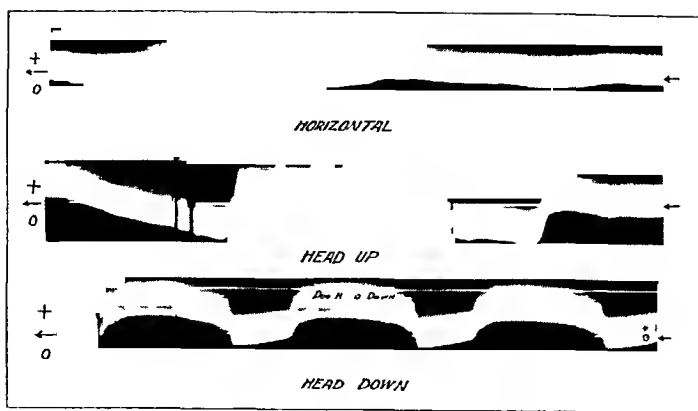


Fig 5 (dog 615) —Photograph on a moving screen of meniscus of the water bubble in a closed manometer The cannula was in the epigastrium The dogs were anesthetized with a barbital derivative The white line through the center was set at atmospheric pressure Note the variations from this line with the change in position Also note that the pressure during the short inspiratory phase is decreased The animal was on its back (Experiment 62, weight of animal, 12 Kg)

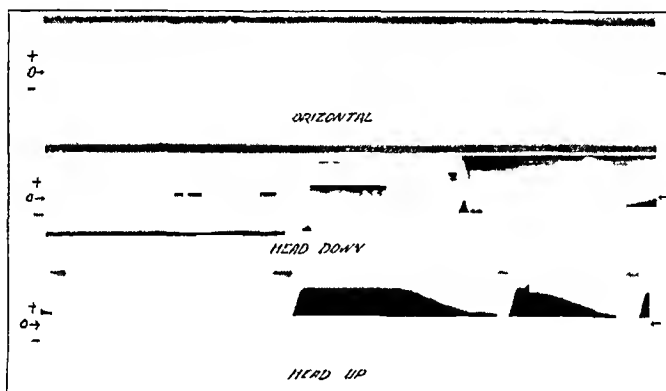


Fig 6 (dog 615) —Photograph showing pressure changes in the lower part of the abdomen with shifts in position Note that in the horizontal position the pressure is above the atmospheric level, as indicated by the white line The pressure decreases with the inspiratory phase Note that the pressure shifts are the reverse of those obtained with the cannula in the epigastrium (fig 5) The animal was on its back (Experiment 62)

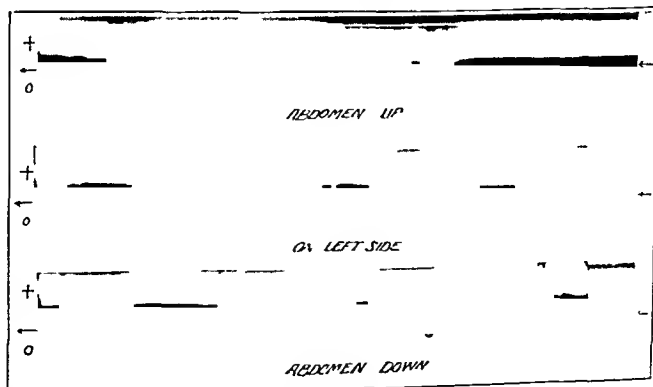


Fig 7 (dog 615) —Photograph showing pressure changes as registered in the Lewis manometer with rotation of the animal in the horizontal position As the animal is turned so that the abdomen is dependent, the pressure increases The cannula was in the lower part of the abdomen (Experiment 62)

above atmospheric pressure (fig 6) However, in many of the animals the pressure fell to a subatmospheric level at the height of inspiration (table 1)

With the animal on its back, a shift to the vertical head-up position caused a marked fall in the intraperitoneal pressure in the upper part of the abdomen and an increase of the pressure in the lower part of the abdomen These results were reversed when the animals were put in a vertical head-down position

In an animal weighing 9 Kg, which was eviscerated and the abdomen filled with water, a similar shift in pressure followed alterations in position In the horizontal position a zero pressure was recorded in the

Intraperitoneal Pressure Variations with Relation to the Relative Positions of the Cannula and the Animal in Three Experiments, Expressed in Millimeters of Water

Position of Cannula	Position of Animal (on Back)	Experiment 49 Dog 476, Wt 8 Kg		Experiment 54 Dog 536 Wt 9 Kg		Experiment 52 Dog 203, Wt 19 Kg	
		Mm Inspi-ration	Mm Expi-ration	Mm Inspi-ration	Mm Expi-ration	Mm Inspi-ration	Mm Expi-ration
Epigastrium	Horizontal	— 47	+ 16	— 26	— 20	— 35	— 32
Epigastrium	Head up	— 58	+ 89	— 155	+ 50	— 67	— 69
Epigastrium	Head down	+ 49	+ 87	— 10	+ 73	+ 75	+ 53
Lower part of abdomen	Horizontal	— 25	+ 8		+ 20	— 30	+ 12
Lower part of abdomen	Head up	+ 103	+ 1	+ 34	+ 130	+ 125	+ 137
Lower part of abdomen	Head down	— 127	— 100	— 46	— 38	— 37.6	+ 15

epigastrium In the head-down position, the pressure was + 108 mm and in the head-up position — 32 mm of water

When the normal anesthetized animal was shifted to a lateral position with the cannula anywhere in the central portion of the anterior abdominal wall, the intraperitoneal pressure increased The rise in the intraperitoneal pressure was even more marked when the animal was turned completely over so that the abdomen was down

With the cannula in the left costovertebral angle and the animal on its back, a positive intraperitoneal pressure was recorded The pressure decreased to a subatmospheric value if the animal was turned so that the abdomen was hanging dependent

The Effect of Abdominal Manipulations on the Intraperitoneal Pressure—Procedures that restricted the movement of the anterior abdominal wall such as pressure of the hand on the abdomen, the application of an abdominal binder or the inflation of the stomach or colon tended slightly to increase the intraperitoneal pressure However, the increase in pressure was barely sufficient to raise it above the atmospheric level when measured in the epigastrium (fig 8)

Pneumoperitoneum—Following the injection of 100 cc of air, an immediate shift from subatmospheric pressure values to values above atmospheric pressure occurred. Subsequent injections of air caused a slight but not proportional, increase in the intraperitoneal pressure.

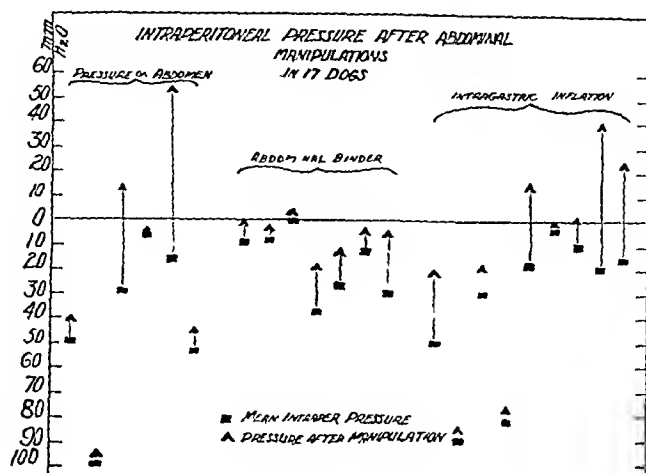


Fig 8—Chart showing effects of pressure on the abdominal wall, an abdominal binder, and of gastric inflation on intraperitoneal pressure. The cross-bar indicates the mean intraperitoneal pressure before, and the arrow point the mean pressure after, the manipulation of the abdominal wall or inflation of the stomach.

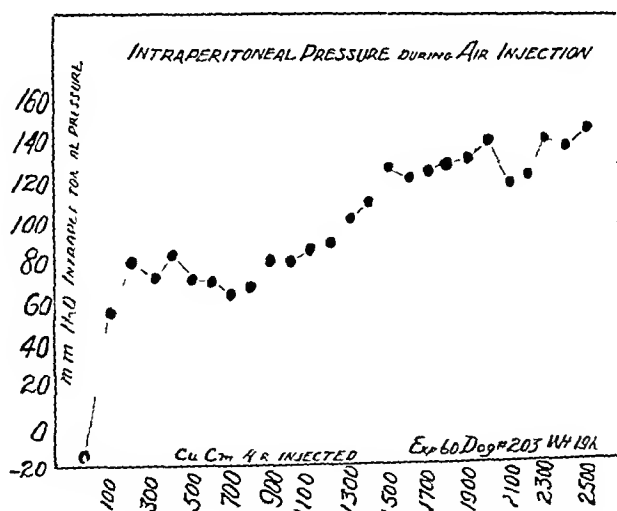


Fig 9—Graph showing the effect on intraperitoneal pressure of repeated injections of 100 cc of air into the peritoneal cavity. Note the stationary pressure values after the first 100 cc was injected.

(fig 9) Air in greater amounts than 100 cc per kilogram of body weight could be injected into the peritoneal cavity before proportional increases in the intraperitoneal pressure followed the additional injections of greater volumes of air.

In the presence of pneumoperitoneum, various manipulations of the abdominal wall or inflation of the stomach by an intragastric balloon caused more marked shifts in the intraperitoneal pressure than was found when the air was not present within the peritoneal cavity (fig 10)

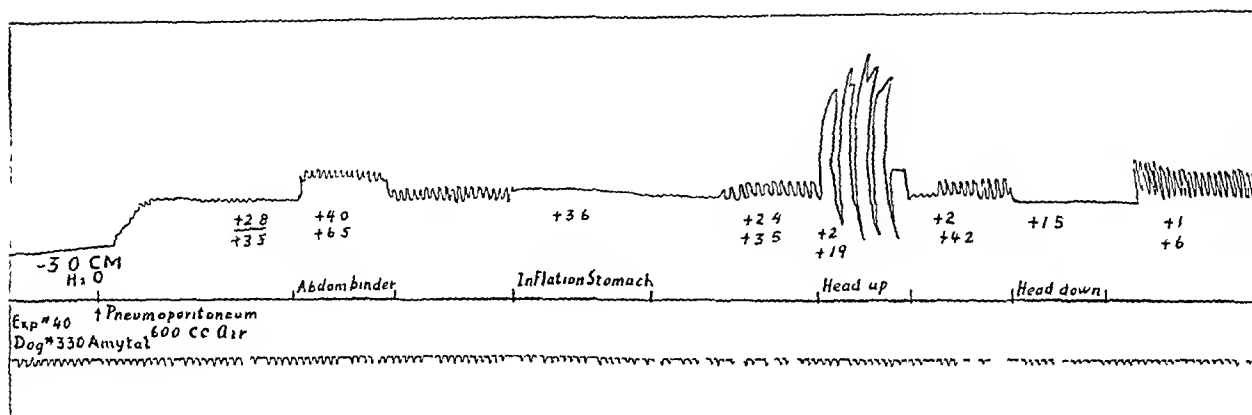


Fig 10—A kymographic tracing showing the effect of the intraperitoneal injection of 600 cc air in a dog weighing 9 Kg. Note the effects of various changes in position and manipulation of the abdomen

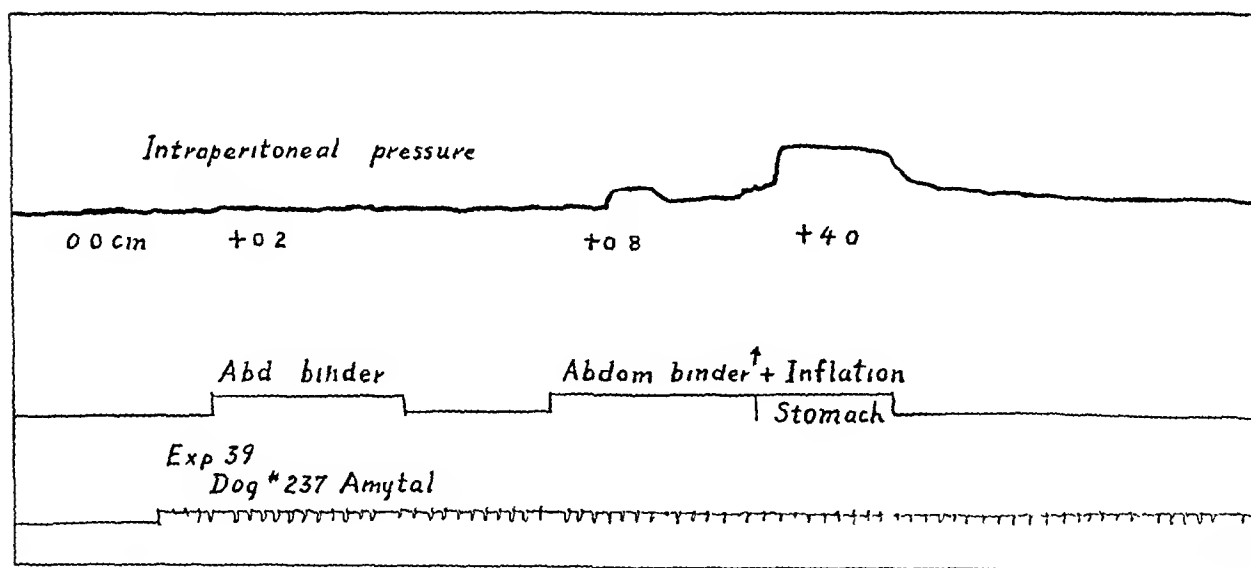


Fig 11—A kymographic tracing showing the slight effect that an abdominal binder has on the intraperitoneal pressure. Note the rise of pressure when a binder and gastric inflation were carried out simultaneously. Note the absence of respiratory excursions by this method.

COMMENT

The pressure within the peritoneal cavity is extremely variable. The relative positions of the cannula and the trunk of the dog determine whether the intraperitoneal pressure value is greater or less than atmos-

phenic pressure The pressure is greatest in the most dependent portions and lowest in the uppermost portions Our observations would tend to substantiate the conception of Krause¹ that the hydrostatic pressure of the contents of the abdominal cavity together with the flexibility of a portion of the abdominal walls determine, for the most part, the pressure within the abdominal cavity The abdomen must be considered as an air-tight space so that, without outside communication, shifts in the position of the contained viscera effect a variation of the pressure in the upper portions of the peritoneal cavity This decrease in pressure is sufficient to maintain a value below atmospheric pressure in the upper part of the abdomen with the animal in the horizontal or erect position

In addition to the hydrostatic factor of the movable viscera, the alteration in the size of the abdomen incident to the phases of respiration is the second most important factor in the consideration of intraperitoneal pressure In contradistinction to the reports of numerous other investigators, we were unable to observe an increase in pressure during inspiration with the animal breathing quietly in any position On the contrary, we found that the intraperitoneal pressure was lessened during inspiration and attained its greatest value during expiration We would conclude from this that the excursion of the costal arches and the increased distensibility (relaxation of the muscles) which occurs during inspiration more than compensates for the descent of the diaphragm Since the subatmospheric pressure in the upper part of the abdomen is dependent on a sagging or "giving way" of the flexible walls below, it seems plausible that the relaxation of the abdominal muscles during inspiration is an important factor in the inspiratory decrease of pressure in the upper part of the abdomen

The fact that the pressure within the peritoneal cavity decreases simultaneously with the decrease in intrapleural pressure (during inspiration) suggests the close relationship between abdominal activity and respiration It also suggests the possibility of interference with pressure variations above the diaphragm by the opening of the sealed cavity below

The ability of the abdominal walls and diaphragm to adjust themselves to conditions tending to raise the intraperitoneal pressure is shown by the minor shifts in pressure incident to the application of abdominal binders or distension of the stomach The fact that the mean intraperitoneal pressure rarely exceeded atmospheric pressure even after gastric distention suggests the importance to respiratory and diaphragmatic activity of the maintenance of subatmospheric pressures in the immediate subdiaphragmatic region

The immediate shift in the intraperitoneal pressure following the injection of small amounts of air and the very slow subsequent increase

in pressure following further injection again point out the extreme flexibility of the abdominal walls. A similar observation was made by Coombs,¹³ who noted pressure changes in the peritoneal cavity of cats during the injection of physiologic solution of sodium chloride. She found that the pressure did not increase in proportion to the fluid injected until a critical point was reached. This was explained on a basis of a reflex "postural activity" of the abdominal musculature.

¹³ Coombs, H. C. The Mechanism of the Regulation of Intra-Abdominal Pressure, *Am J Physiol* **61** 159 (June) 1920

THE DIMENSIONS AND GROWTH OF THE PALATE IN THE NORMAL INFANT AND IN THE INFANT WITH GROSS MALDEVELOPMENT OF THE UPPER LIP AND PALATE

A QUANTITATIVE STUDY *

WILLIAM T PEYTON, MD

MINNIAPOLIS

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The investigator should consider himself fortunate if he finds a field of investigation in which opinions and estimates have long been expressed and in which more recently the fundamentals have been subjected to debate in a tone of controversy. He should be especially pleased if he takes up this subject with the intention of applying the comparatively newer quantitative methods of analysis and finds that these methods have not yet been tried in this particular field, although they are well suited for it.

* Submitted for publication, July 29, 1930

~ A thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy

From the Department of Surgery, University of Minnesota

Investigation of the quantity and position of the tissue in children with cleft palate answers the foregoing hypothesis. For years opinions have been expressed to the effect that there is a deficiency of tissue in cases of congenital clefts of the upper part of the face and jaw. Brophy (1907) brought controversy when he said that all tissues are present. Since this statement was made, it has been refuted by opinions based on clinical estimates or made on a few measurements, taken for the most part on the facial skeleton rather than directly on the palate.

The solution of this question, namely the amount and disposition of the tissue in the cleft palate, is essential to the selection of plans for the surgical repair of these clefts. Fundamentally, there are three principal types of operation typified by the operations of Krimei, Warren and Brophy for clefts of the alveolar process and palate, all of which have undergone many modifications by other surgeons. The operation of Krimei, better known as the flap operation of Lane, is similar to other plastic flap operations in general surgery used to restore defects which are due to loss of tissue. The Warren-von Langenbeck operation

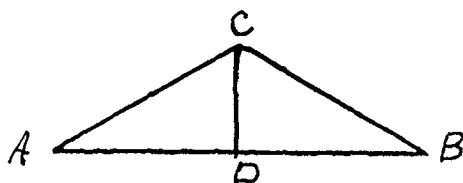


Fig. 1—Measurements of palate as they were determined by Alkan

is similar to other plastic operations performed for the restoration of defects caused by separation, but without loss of tissue. The Brophy operation is based on the assumption that the cleft is due to lateral separation of normally developed tissue.

This study is undertaken with no attempt to prove any expressed opinion or to support a personal theory.

LITERATURE

THE NORMAL PALATE

Quantitative growth of the normal palate has been subjected to only superficial investigation. Alkan measured the width and length of the hard palate with a calipers and calculated the height. He took the diameter or width (fig. 1 AB) between the first and second premolar and also between the first and second molar teeth from the inner margin of the gum except in new-born children where only one measurement of the width was taken and this at approximately the middle of the alveolar process. From this same point on each side of the alveolar process he took measurements AC and CB (fig. 1) where C is located

at approximately the center of the arch of the palate. The height of the palate CD was then calculated from the known values for AC , CB and AB .

The material measured by Alkan included thirty-five infants from 1 to 9 days of age and also one child 90 days old. No trend of growth is demonstrated in these measurements. The averages were as follows: width, 2.7 cm, length, 3.2 cm, and height 1.2 cm. He computed width-height indexes to compare with similar indexes computed for adult

TABLE 1—*Dimensions of Palates of Children as Determined by Alkan*

Age, Days	Sex		Skull			Palate		
	Male	Female	Length, Cm	Width, Cm	Width of Face, Cm	Width, Cm	Length, Cm	Height, Cm
1		1	11.7	8.8	7.0	2.6	3.4	1.5
1	1		12.1	9.1	7.3	2.6	3.1	1.0
1		1	11.9	9.7	7.1	2.8	3.4	1.05
1		1	12.0	9.4	7.2	2.9	3.4	1.3
2		1	9.7	8.0	5.85	2.1	3.2	0.8
2		1	11.6	9.0	6.5	2.5	3.2	1.2
3		1	11.6	9.5	7.3	2.9	3.5	1.3
3		1	11.2	8.3	6.6	2.6	3.3	1.3
3		1	12.0	8.8	7.1	2.8	3.0	0.95
3		1	11.5	9.3	7.1	2.7	3.1	1.4
3		1	11.9	9.0	7.1	2.4	3.4	1.3
3		1	11.8	9.7	6.9	2.4	2.9	1.3
4	1		10.7	8.6	6.4	2.3	3.1	0.9
4		1	12.0	8.9	6.8	2.4	3.3	0.8
4	1		11.6	8.8	7.2	2.7	3.1	1.4
4	1		13.0	9.8	7.3	3.0	3.1	1.1
4		1	11.3	8.5	6.9	3.0	2.9	1.0
4		1	11.7	9.2	7.4	2.8	3.3	1.4
5	1		11.6	9.3	6.8	3.1	3.5	0.9
5	1		11.5	9.3	7.2	2.9	3.2	1.3
5	1		11.9	9.0	6.6	2.6	3.0	1.1
5	1		11.6	8.6	6.7	2.8	3.0	1.3
6		1	11.3	9.3	7.2	2.6	3.6	1.2
6		1	10.5	7.6	6.5	2.5	3.4	1.1
6	1		12.0	9.0	7.2	2.6	3.2	1.3
6	1		11.4	8.8	7.2	2.8	3.3	1.3
7	1		12.2	9.6	7.3	3.0	3.3	0.95
7	1		11.7	9.3	7.5	2.8	3.0	1.1
8	1		11.9	9.0	6.7	2.5	3.2	1.1
8		1	11.7	8.9	6.9	2.7	3.0	1.1
8	1		13.1	9.4	7.2	2.9	3.5	1.3
8	1		12.3	10.4	7.3	3.0	3.4	1.3
9		1	11.4	9.1	6.5	2.6	3.0	1.0
9		1	11.9	8.9	7.0	2.6	3.1	1.3
9		1	12.1	9.6	7.4	2.9	3.2	1.3
90	1		11.2	8.7	6.2	2.8	2.9	1.1

material and concluded that the palate of the new-born infant is relatively short and high. His measurements are recorded in table 1.

Denzel took some measurements on the palates of children under 1 year of age by making impressions of the palate, and from these impressions he made dental casts. Measurements were read from the dental cast with the surveying apparatus of Stanton. This surveying apparatus is an orthoscopic apparatus with which it is possible to locate and read the position of a point in three dimensions. It is therefore used to make orthographic projections from models and for measuring elevations. For width, Denzel took the widest point of the alveolar process, and for height the highest point of the arch of the palate.

These are the same measurements which have been taken in the present investigation. The results as determined by Denzer are recorded in tables 2 and 2a. The averages of his measurements were width, 30.9 mm and height, 8.79 mm.

W. K. Connell read a paper before the Anatomical Section of the British Medical Association in 1922 on the "Form of the Palate in Children." He took an impression of the upper dental arcades in plasticine and studied the variations in shape and determined in normal and abnormal conditions the changes which took place during growth,

TABLE 2—*Dimensions of Palates of Children as Determined by Denzer*

Age	Greatest Width, Mm	Greatest Height, Mm	Age	Greatest Width, Mm	Greatest Height, Mm
3 months	32.5	8.7	5 months	32.0	8.2
4 weeks	27.5	8.0	5 months	30.5	10.0
4 weeks	29.0	8.0	5 months	30.0	8.6
12 days	30.0	11.3	5 months	28.5	9.0
6 weeks	28.5	8.0	6 months	31.5	9.7
6 weeks	30.0	9.9	6 months	30.5	8.6
6 weeks	30.5	9.6	6 months	28.5	7.2
7 weeks	28.0	7.4	7 months	31.5	7.7
2 months	28.0	9.5	7 months	30.0	8.7
2 months	27.0	7.7	7 months	32.0	8.1
2 months	31.0	10.1	8 months	33.5	8.8
2 months	28.5	7.5	8 months	31.5	9.9
3 months	32.0	7.4	9 months	35.0	8.0
3 months	32.5	8.7	9 months	32.5	7.1
4 months	33.0	9.7	10 months	36.0	9.8
4 months	32.0	9.4	11 months	30.0	9.5
4 months	30.0	8.7	11 months	34.0	9.4
4 months	34.0	9.5	11 months	33.0	8.1
4 months	32.5	10.0			

TABLE 2a—*Average Dimensions at Different Ages*

Age	Number of Cases	Greatest Width, Mm	Greatest Height, Mm
1 to 3 months, inclusive	13	29.4	8.7
4 to 6 months, inclusive	12	31.0	9.0
7 to 11 months, inclusive	11	32.6	8.5
All children under 1 year	29	30.9	8.89

also the relation of the size of the arch to the state of development of the child. He found that, "There was no connection between the size of the child and the shape of the palate, nor was there any alteration in the arcade in children with adenoids."

Buser measured the width, height and length of the palate in 514 persons all of whom were over 15 years of age. He used special instruments, with which he took readings directly from the palate, without the use of impressions or casts. Two measurements of width were taken—one at the first premolar tooth and the other at the first molar tooth. Height was taken as the highest point of the arch of the palate in relation to the occlusive surface of the teeth. Length of the palate was taken as a direct line measurement from the space between

the medial incisors in front to the posterior edge of the hard palate. Division according to sex was made in all of his tables, and still further divisions according to age were made in some of his tables. The data on persons from 15 to 17 years of age are included in one table, and on all above this age are included in the second table. The male palate in each of its dimensions is approximately 1 mm greater than those of the female, according to his observations, and there is a slight increase in size after the fifteenth year. The approximate dimensions of the adult palate taken from the tables of Buser are as follows: width (at first molar), 48 mm, height, 21 mm and length, 54 mm. Table 3 is copied from Buser.

Shaw measured the width, height and length of the palate in adults. His results were: height 14.2 mm, length, 50.8 mm, and width (at first molar), 35.5 mm.

TABLE 3—*Dimensions of Palates as Determined by Buser*

Age of Individuals Measured	Dimension	Males		Females	
		No. Cases Measured	Average Size, Mm	No. Cases Measured	Average Size, Mm
15 years of age and over	Palate width, first premolar	237	37.5	237	36.0
	Palate width, first molar	213	48.6	186	46.9
	Palate height	237	21.6	237	20.2
	Palate length	254	54.7	257	52.7
15 to 17 years of age	Palate width, first premolar	17	37.7	75	35.7
	Palate width, first molar	12	47.9	53	46.5
	Palate height	17	20.8	75	19.6
	Palate length	17	53.2	75	52.8
18 years of age and over	Palate width, first premolar	240	37.4	182	36.1
	Palate width, first molar	201	49.6	133	47.2
	Palate height	240	21.7	182	20.4
	Palate length	237	54.8	182	52.7

Gustav Franke measured a large series of palates at different ages. The width of the palate, measured at the posterior border of the first molar tooth, as determined by Franke is as follows: 2 to 7 years, 41.1 mm, 8 to 13 years, 45.9 mm, 14 to 21 years, 48 mm, 22 to 29 years, 49.4 mm, 30 to 50 years, 50.2 mm. The length of the palate, according to Franke's figures, was 26.8 mm at birth and 52.8 mm in the adult, or approximately a twofold increase between birth and maturity.

THE MALDEVELOPED PALATE

Quantitative studies of growth and of the amount and disposition of tissue in the cleft palate are meager, but there are many opinions based purely on clinical observation or on the writings of others.

The measurements which have been taken to estimate the quantity of tissue or the spread of tissues in the palate have for the most part been taken indirectly, either skull measurements were taken to determine the breadth of the facial portion of the skull, or to determine the dis-

tance between the hamular process, or between other similar bony points of the facial skeleton. These measurements have been made largely on the macerated skull rather than on the living child.

Some measurements made by Kirkham on skulls in the Hunterian Museum of London are given in table 4. The greatest abnormality in dimensions of cleft palates according to these figures, is in the distance between the hamular processes.

Skull measurements made by Wardill on museum specimens with and without cleft palate, together with similar measurements taken by Veau and quoted by Wardill are recorded in table 5. Wardill concluded from these measurements of the bony parts that there is associated with

TABLE 4—*Skull Dimensions as Determined by Kirkham*

Age	Distance Between Posterior Palatine Foramina, Mm	Distance Between Hamular Processes Mm	Distance From Hamular Process to Posterior Palatine Foramina, Mm	Distance Between Tuberosities, Mm
Normal children				
Birth	17.5	18.0	6.0	27.0
2 months	19.5	22.0	5.5	30.0
10 months	20.0	ns*	ns	30.5
8 months	22.0	22.5	7.5	29.5
12 months	23.0	23.0	9.0	33.5
19 months	22.5	ns	ns	35.0
2 years	21.5	ns	ns	33.0
2½ years	23.0	ns	ns	27.5
2½ years	23.5	24.5	9.0	27.0
3 years	22.0	24.0	9.0	37.5
3½ years	22.5	27.0	10.0	36.5
4 years	22.0	29.0	12.0	39.0
5 years	25.0	27.5	12.0	36.0
5¾ years	15.0	28.0	11.0	27.5
6 years	22.5	ns	ns	37.5
8 years	27.0	32.0	12.0	40.0
Normal				
Average adult	30.0	34.0	12.0	54.0
Cleft palate				
Adult	40.0	41.0	12.0	54.5
Nubian woman	10.0	46.0	10.5	55.0

* Hamular process was missing and therefore measurement was not taken.

cleft palate a small but definite increase in the transverse diameter of the nasopharynx.

Izard has determined that there is a rather constant relationship in the adult between the transverse diameter of the palate and the bizygomatic diameter of the facial portion of the skull. This relationship is approximately 1:2 but it apparently does not hold for infants in which the bizygomatic distance is considerably less than twice the transverse diameter of the palate. The transverse diameter of the palate and the bizygomatic diameter of the skull as determined by Ruppe are included in table 6. Ruppe concluded that for infants these measurements of skulls with cleft palate are quite similar to those of normal skulls and therefore that there is no evidence of separation of the maxilla in the cleft palate.

Superimposing tracings of the alveolar curves of the maxilla and mandible, J E Thompson concluded that the maxillary tuberosities have not been much displaced in cleft palate, since he found the maxillary process at this point seldom more than 1 mm greater than that

TABLE 5—Measurements Compiled by Wardill

Nasion to Occipital Point, Mm	Transverse Diameter, Mm	Transverse Hamuli, Mm	Nasion to Occipital Point, Mm	Transverse Diameter, Mm	Transverse Hamuli, Mm
180 0	150 0	33 5	176 0	148 0	35 0
162 0	149 0	43 0	171 0	133 0	28 0
156 0	133 5	92 0	160 0	133 0	33 0
127 0	117 0	27 0	151 0	124 5	23 0
123 0	103 0	24 0	148 0	124 0	26 0
122 0	101 0	24 5	133 5	117 0	23 5
121 0	103 0	31 0	120 0	92 0	21 0
117 0	111 0	31 0	112 0	90 0	18 5
101 0	82 0	23 0	107 0	84 0	22 0
100 0	94 0	26 0	103 0	90 0	19 0
93 5	88 0	24 5	99 0	82 5	19 5
93 0	83 0	25 0	96 0	82 0	17 5
*Glabella to Occipital Point, Mm			*Glabella to Occipital Point, Mm		
175 0	128 0	41 0	178 0	149 0	34 0
187 0	150 0	42 0	190 0	147 5	36 0
187 0	145 0	43 5	195 5	191 5	32 5
169 0	125 0	39 5	180 0	141 0	30 0

* Glabella to occipital point substituted here for nasion to occipital point distance because in the skulls with cleft palate a large part of the calvarium had been removed

TABLE 6—Skull Dimensions as Determined by Ruppe

	Transverse Diameter of Palate, Mm	Bizygomatic Diameter, Mm	Twice the Bimaxillary Distance, Mm
Skulls of normal infants	14	23	28
	16	26	32
	17	26	34
	17	30	34
	18	30	36
	19	33	38
	21	34	42
	25	46	50
	27	44	54
	27	48	54
	28	48	56
	33	56	66
	33	57	66
	35	62	70
Skulls of infants with cleft palate	60	100	120
	48	85	96
	45	70	90
	32	78	64
	43	86	86
	40	66	80
	47	92	94
	50	82	100

of the mandible, but the most prominent curve of the alveolar processes he found 2 or 3 mm displaced or spread

Trendelenburg concluded that the facial portion of the skull is wider than normal when the palate is cleft. He took measurements on the width of the choanae, the distance between the infra-orbital foramen

and between the zygomaticomaxillary suture of each side on skulls with and without cleft of the palate, and found that these dimensions are greater in persons with cleft palate.

Alex Lindberg stated that measurements of normal patients and patients with cleft palate demonstrate the mesopharynx to be from 0.5 to 1.5 cm greater in the latter.

Opinions based in part or entirely on observation, rather than measurement, are found in the literature on maldevelopments of the lip and palate. These opinions are readily divisible into two groups completely at variance with each other. In one group are those who believe that all the tissue is present, and in the other are those who believe there is an actual deficiency of tissue due to deficient development, arrested growth or atrophy. Outstanding among the former and apparently the first to press this opinion was Brophy (1907), who maintained that children who have congenital malformation of the palate, with rare exceptions, have the normal amount of tissue in the palate. Brophy maintained that when the margins of the cleft have been brought into contact, the upper jaw is then restored to its normal breadth and to its proper relation to the lower jaw. There are few exceptions, and he further said that other writers have been unconscious of the fact that as a rule the bones are not deficient in structure or incomplete in development.

Veau also expressed the belief that the parts are normal, or if less than normal, that they have between them the ability to reproduce the normal amount of palate tissue. He stated that they are developed as a normal palate, but that it becomes abnormal only because of lack of coalescence.

The opinion of the majority falls in the second group, which holds that there is not a normal amount of tissue in the cleft palate.

Arthur Keith (1909) quoted Brophy to the effect that there is no deficiency in the tissue of the cleft palate. But Keith stated that this was not the case in the specimens that he had examined. He examined the palates of three adults with clefts and found the clefts on the average 20 mm wide, the average breadth of the palate was 64 mm, and this, he said, demonstrates that the bony parts of these palates were from 10 to 15 mm less than normal. In new-born children, according to Keith, the deficiency affects the inner or marginal area of the palate but it does not amount to more than 3 mm on each side. He admitted that he is not able to say whether or not the cleft continues to increase after birth, but judging from the width of the cleft of the adult palate, he concluded that they do not continue to separate at the rate after birth that they did before birth.

Wintermiz is of the opinion that the halves of the cleft palate are rudimentary and that their relative growth is not in proportion to that

of the oropharyngeal cavity, wherefore in later years the cleft is not only wide, but that this lack of development causes a relatively short soft palate after repair, and therefore is the cause of poor speaking function after repair. He is of the opinion that this lack of development in relation to the skull is especially marked in the soft palate.

According to Trendelenburg, there is a lack of normal development not only of the palate on the side of a unilateral cleft, but the growth of the entire jaw on this side is retarded. Failure to recognize the short side of the alveolar process as a part and not a complete half of the process is apparently the basis of this opinion.

Ernest Frazer said there is no question that an extra protrusion of the frontonasal region and elongation of its septal portion does occur, but it is possible that a certain amount of the appearance of protrusion is really due to a deficiency of the maxillary mass placed beside it. He is of the opinion that "accurate measurements, however, under many conditions are necessary in quantity."

Wardill, in speaking of the cleft palate, said, that there is less than the normal amount of soft tissue, and that this has been used to bridge an abnormally wide nasopharynx. J. F. Esser said that one should not forget that there is practically always a deficit of material.

COLLECTION OF DATA

MEASUREMENTS TAKEN

The data consist essentially of two parts (1) general body and head measurements and (2) palate measurements. Weight and standing and sitting height were the general body measurements taken. Twenty-three head measurements were taken, but are not all incorporated in this report, seven of these head measurements were bilateral. Crown-heel length and fronto-occipital diameter are the only body and head measurements used in this report. The body and head measurements were taken in the usual manner. Details of procedures in obtaining those used in this study are given in the following paragraphs. Special technic for obtaining palate measurements were worked out the details of which are subsequently given.

METHOD OF OBTAINING MEASUREMENTS

The crown-heel length was taken with the Martin anthropometer, the straight attachments being used, and the frontal-occipital diameter was taken with Martin curved arm calipers.

All the measurements on the palate were taken from dental casts and dental molds. Kerr perfection impression compound was used to make these dental casts. A dental tray could not be found on the market small enough to use in the first year of life. To obtain a suitable tray, an impression was made of the upper jaw of a new-born infant, and a dental tray was made up from this.

The impression compound was softened in warm water and applied to the palate on the dental tray cold water on a sponge was applied to harden the material quickly before its removal from the mouth. These impressions were flowed up in dental plaster of paris in the usual manner to obtain a plaster of paris mold (dental cast) of the palate. One of the most difficult points to determine was the medial edge of the palate plate in cases with cleft. As a rule, however,

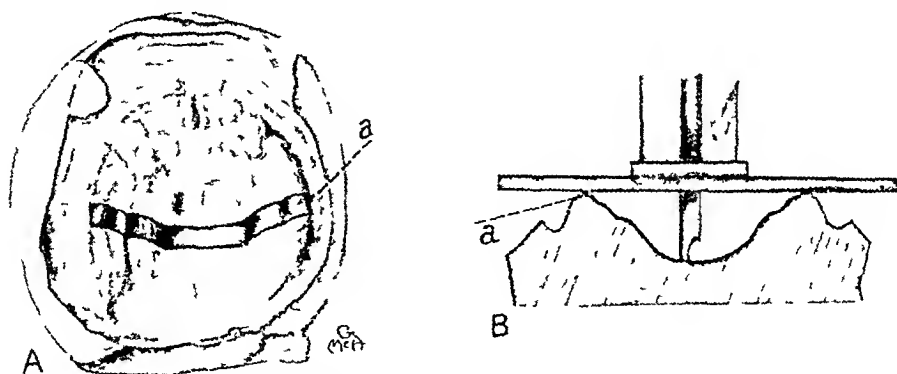


Fig 2—Method of taking the surface width and height of the normal palate. In *A*, the lead foil is applied at the widest part of the alveolar process to obtain the surface width of the palate. *B* is a cross-section of the palate to show the method of measuring the height of the palate. *a* shows measurement at the highest point of the alveolar process.

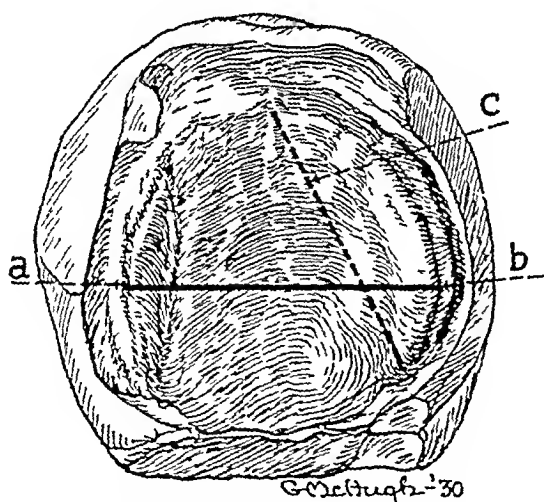


Fig 3—Measures taken for the normal palate. *a*, the widest transverse diameter of the palate measured to the highest point of the alveolar process (*b*), *c*, the chord of the alveolar process.

this was well demarcated by a line representing the transition from the squamous epithelium of the oral cavity to the ciliated epithelium of the nasal cavity.

Four dimensions common to both the normal and maldeveloped palate were taken and in addition the width of the cleft was read in the maldeveloped palates. Those common to both the normal and the cleft palate were (1) widest transverse diameter (2) surface width of palate (3) height of palate and (4) the chord of the alveolar process which is referred to in the text as the length of

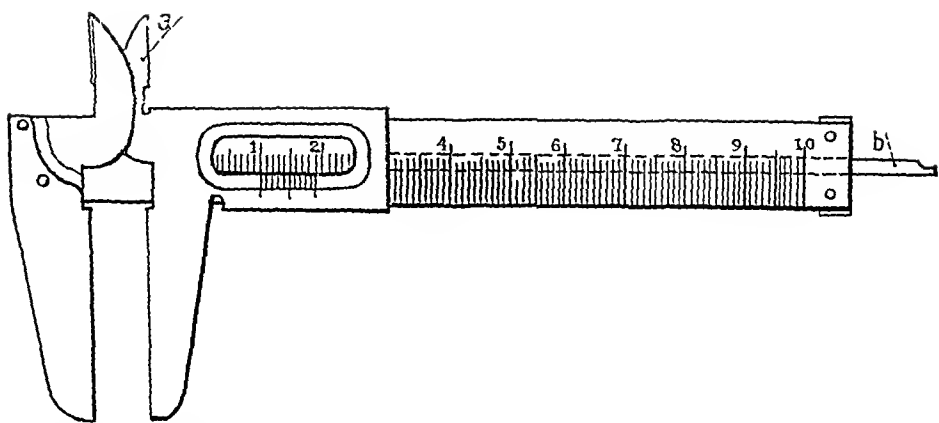


Fig 4—Instrument used for taking measurements on the palate *a* indicates the blade used for measuring the width of the cleft, and *b*, the sliding bar used for measuring the height of the palate

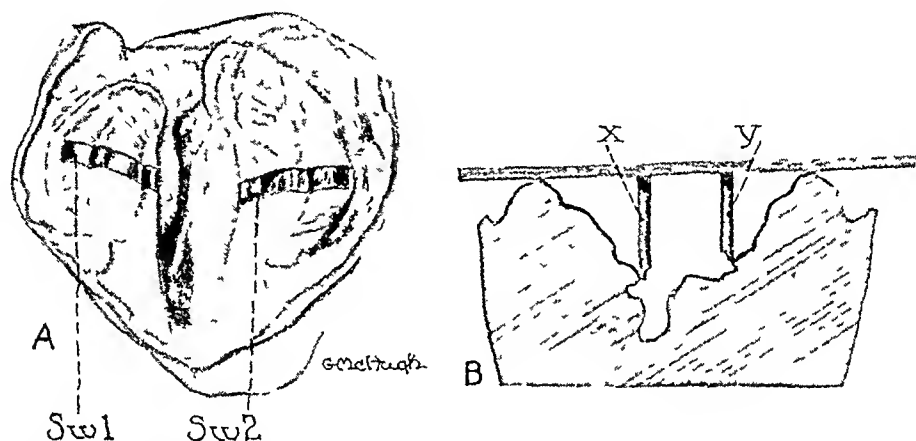


Fig 5—Method of taking the surface width and height of the palate in unilateral clefts of palate In *A*, *Sw* indicates the surface width of the palate, $Sw1 + Sw2 = \text{total } Sw$ *B* is a cross-section of the palate, $\frac{X + Y}{2} = \text{height of palate}$

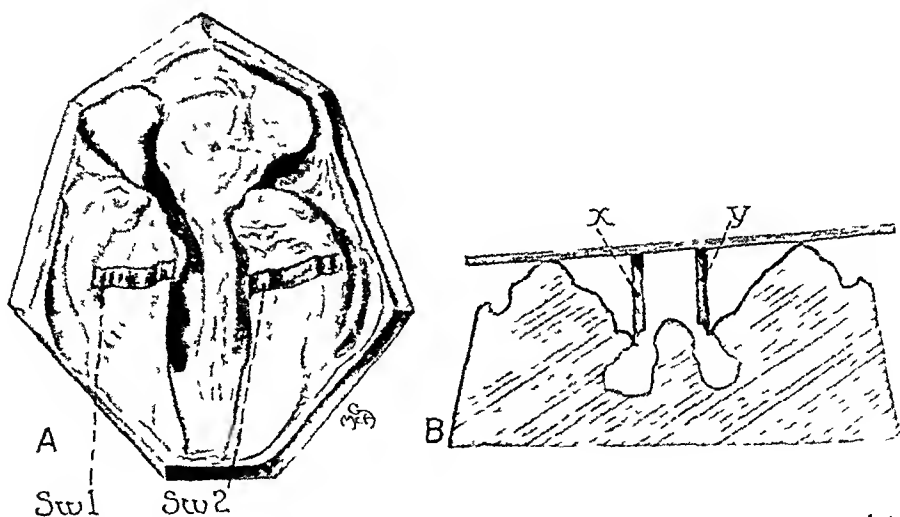


Fig 6—Method of taking the surface width and height of the palate in bilateral clefts of the palate In *A*, *Sw* indicates the surface width of the palate, $Sw1 + Sw2 = \text{total } Sw$ *B* is a cross-section of the palate, $\frac{X + Y}{2} = \text{height of palate}$

alveolar process The method of taking these measurements in the normal palate is illustrated in figures 2 and 3, and for the cleft palate in figures 4, 5, 6 and 7

In general, the descriptive name designates what these measurements are, but the end-points utilized and the exact method of taking them is as follows The widest transverse diameter of the palate was taken in approximately the coronal plane, using the middle of the alveolar process as end-points The surface width

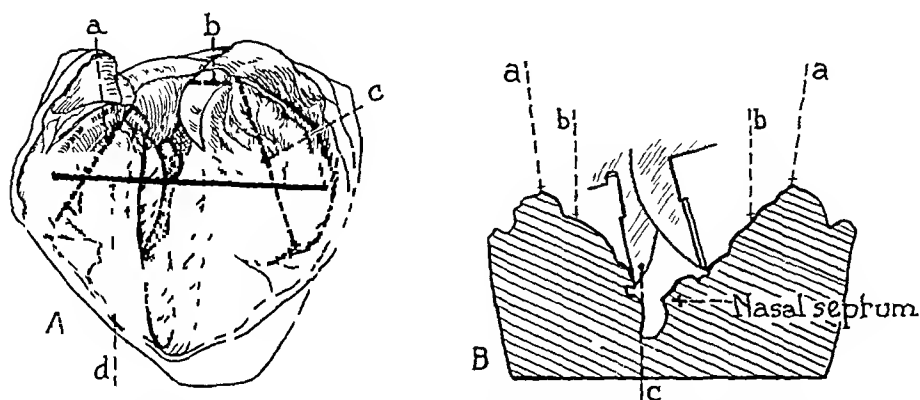


Fig 7—Measures taken for the widest transverse diameter, length of the alveolar process and the width of the cleft in unilateral clefts of the palate In *A*, $a + b$, and c indicates the chords of the alveolar process, d , the widest transverse diameter of unilateral cleft palate In *B*, a indicates the alveolar process of the palate, b , the plate of the palate, and c , the method of measuring the width of unilateral cleft palate

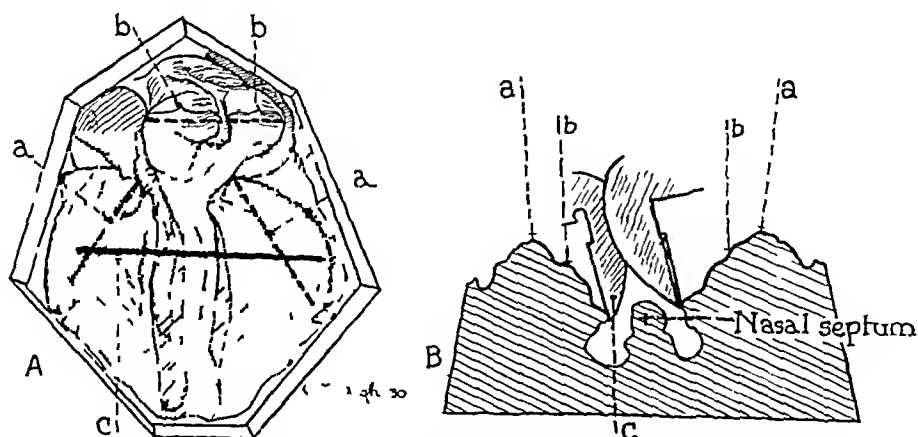


Fig 8—Measures taken for the widest transverse diameter, the length of the alveolar process and the width of the cleft in bilateral clefts of the palate In *A*, $a + b$ indicates the chord of the alveolar process, and c , the widest transverse diameter of a bilateral cleft palate In *B*, a indicates the alveolar process of the palate, b , the plate of the palate, and c , the method of measuring the width of a bilateral cleft palate

of the palate was taken in approximately the same coronal plane as the widest transverse diameter and with the same end-points but in the following manner Thin sheet lead was cut into strips from 1 to 2 mm wide, and this strip pressed firmly against the palate so that it assumed the shape of the palate surface includ-

ing all its irregularities After the strip had been so pressed into position, it was cut at the end-points of the measure, that is, where the strip passed over the mid-portion of the alveolar process The strip was then removed, pressed out on a flat surface to remove all irregularities, and with a calipers this straight piece of metal was measured This dimension is referred to as the surface width of the palate In the cleft palate, two strips were used, one for each plate of the palate, and here the end-point for the medial edge of the plate was taken at the point of transition of the squamous epithelium of the oral cavity into the ciliated epithelium of the nasal cavity

The height of the palate was taken by placing a rigid metal bar across the palate at its deepest portion, and the distance from the upper surface of this metal bar to the deepest point of the mold was read The width of the transverse bar was subtracted from this reading and the remainder taken as the actual height of the arch of the palate A true curvilinear measurement of the length of the alveolar process was not taken, but instead a straight line measurement, the arc of the alveolar process was measured to estimate its length It was taken from the midpoint anteriorly to the posterior end of the alveolar process on each side The measurement for each side was recorded separately, but the average of both sides has been used in this analysis This measurement could not be taken directly on the short side of the unilateral clefts, nor directly on either side of the bilateral cleft, but was, in the unilateral cases, taken as the sum of the short side plus one-half the width of the premaxilla, and in the bilateral clefts as the length of one side plus one-half the premaxilla The width of the cleft was taken with a calipers as illustrated in figure 3, at the point of the widest separation of the medial edge of the plates of the palate

SELECTION OF MATERIAL

The material consists essentially of two groups, namely, normal children and maldeveloped children, each group covering approximately the same growth period

Ninety-one normal children are included in this material, fifty-one of whom are females and forty are males This division as to sex was entirely chance since no attempt was made at selection In age they ranged from a new-born (premature) infant to a child 362 days of age and in length from 45.7 cm crown-heel length (a premature infant) to 75.7 cm crown-heel length All were presumably normal children They were obtained from (1) the Out-Patient Dispensary at the University Hospital, (2) the Infant Welfare Clinics of Minneapolis, (3) various homes for illegitimate children and (4) hospital boarders Physically abnormal children were not accepted for measurement

In collecting the maldeveloped material, only children with complete clefts of both the alveolar process and hard and soft palate (that is, group III according to the Ritchie-Davis classification) were accepted One exception to this general rule was made, this was a child with a complete unilateral cleft of the lip and process, but with a normal hard palate and soft palate Twenty-six abnormal cases were obtained, and two of these were measured twice, with an interval of several weeks between measurements This makes a total of twenty-eight sets of measurements, and represents the material coming to the University Hospital between January, 1928, and March, 1930, and in addition, eight others who were during this period private patients of Dr Ritchie Included in this abnormal material are six females and twenty males varying in age from a premature infant to a

child 425 days of age and in length from 47.5 cm crown-heel length (a premature infant) to 75.1 cm crown-heel length. The maldeveloped material is listed in table 7. The arrangement of this table is according to increasing crown-heel length, for the males, and females, respectively.

DATA LISTED

All data are listed in table 8. Division of the material is here made into normal and maldeveloped children, and each of these groups are divided according to sex. The order of listing is according to increasing crown-heel length. Age in days and weight in grams are included in this table, although they were not utilized in the present analysis of this material.

TABLE 7—*Maldeveloped Children*

Crown heel Length, Cm	Age, Days	Description of Lesion
Males		
47.5	11*	Bilateral complete cleft of lip, process and palate
50.0	10	Right complete cleft of lip, process and palate
50.3†	3	Bilateral complete cleft of lip, process and palate
50.9	58	Left complete cleft of lip, process and palate
51.4	42	Left incomplete cleft of lip, complete cleft of process and palate
51.6‡	16	Right incomplete cleft of lip, complete cleft of process and palate
51.7	47	Right unilateral complete cleft of lip, process and palate
52.0	47	Right unilateral complete cleft of lip, process and palate
52.1	28	Bilateral complete cleft of lip, process and palate
52.3†	25	Bilateral complete cleft of lip, process and palate
52.7	46	Bilateral complete cleft of lip, process and palate
53.6‡	40	Right complete cleft of lip, process and palate
56.8	56	Left incomplete cleft of lip and process, complete cleft of palate
56.9	121	Right complete cleft of lip, process and palate
56.9	21	Left complete cleft of lip, process and palate
57.0	71	Right complete cleft of lip, process and palate
57.8	89	Left complete cleft of lip and process, incomplete cleft of palate
59.0	76	Bilateral complete cleft of lip, process and palate
59.2	101	Right incomplete cleft of lip, complete cleft of process and palate
59.5	110	Bilateral right complete cleft of lip, process and palate, left incom- plete cleft of lip, process and palate
63.4	190	Left complete cleft of lip, process and palate
75.1	391	Left complete cleft of lip, process and palate
Females		
52.2	41	Right incomplete cleft of lip, complete cleft of process and palate
52.8	71	Bilateral complete cleft of lip, process and palate
58.9	81	Left complete cleft of lip, process and palate
59.7	95	Left incomplete cleft of lip, complete cleft of process and palate
63.7	246	Right complete cleft of lip, process and palate
66.1	186	Left complete cleft of lip, process and palate

* Premature infant

† and ‡, same child measured a second time

ANALYSIS OF DATA

TEST FOR NORMALITY

It is, of course, essential that the dimensions of the cleft palate be compared with the dimensions of the palate in normal children of approximately the same size. To check this, all the material, both normal and abnormal, was compared with a much larger series of normal children (approximately 600) collected by Dr. L. Richdorf.¹ They were

1 Richdorf, L. A Quantitative Study of Growth of the Normal Infant in the First Year, unpublished thesis for degree of Doctor of Philosophy, University of Minnesota

TABLE 8—Table of Data

Crown Heel Length, Cm	Age, Days	Weight, Gm	Fronto occipital Diameter, Cm	Widest Transverse Diameter of Palate, Cm	Actual Surface Width of Palate, Cm	Height of Palate, Cm	Length of Alveolar Process, Cm
Males (Normal)							
49 0	2	3,020	11 1	3 00	3 50	0 72	2 90
49 2	1	3 355	12 3	3 20	3 60	0 93	2 98
49 3	16	3,015	12 0	3 25	3 90	0 97	3 05
51 5	4	3,115	11 7	3 27	3 80	0 94	2 70
51 7	16	3,484	11 7	3 38	3 81	0 96	3 07
52 1	14	3,555	12 6	3 30	3 90	0 98	3 25
52 6	53	3,975	12 5	3 20	3 70	0 81	3 00
52 7	0	3,760	11 2	3 40	3 80	0 81	3 17
52 9	6	3,150	12 2	3 40	3 85	0 80	2 98
53 4	5	4,105	12 1	3 45	4 00	0 80	2 90
53 7	66	4,020	12 5	2 90	3 40	0 71	2 70
54 2	20	3,960	12 6	3 00	3 70	0 94	3 05
54 3	36	4,000	13 5	3 42	4 00	0 86	3 15
54 6	37	4,705	13 1	3 45	4 20	0 85	3 28
56 6	48	4,045	11 7	3 35	4 10	0 96	3 20
56 8	86	4,545		3 32	3 90	0 87	3 10
57 9	87	4,760	12 7	3 10	3 80	0 93	2 78
58 9	124	6 170	13 3	3 60	4 20	0 91	3 18
59 0	119	5,675	12 6	3 20	4 30	0 85	3 00
59 0	136	5,395	13 8	3 50	3 65	1 00	3 05
59 3	45	5,429	13 8	3 60	4 30	0 93	3 28
59 9	105	6,790	11 8	3 50	4 25	1 04	3 25
60 1	113	4,750	13 4	3 35	4 00	0 86	3 18
60 4	101	6,505	13 8	3 42	3 80	0 79	3 28
60 5	93	5,670	13 3	3 55	4 35	1 01	3 35
61 7	140	7,045	14 0	3 40	4 00	0 91	3 25
62 9	141	6,255	13 4	3 42	4 22	1 12	3 38
63 6	123	6,805	12 7	3 60	4 00	0 72	3 25
64 1	135	6,275	13 2	3 40	4 02	0 84	3 53
65 1	219	8,940	15 3	3 40	3 90	0 76	3 24
65 7	193	7,300	14 4	3 60	4 17	0 95	3 17
65 7	141	7,810		3 70	4 40	0 96	3 55
66 6	168	6,700	12 6	3 70	4 30	0 94	2 95
66 8	225	8,630	14 2	3 60	4 32	1 00	3 36
67 0	179	7,850	12 8	3 60	4 50	1 17	3 00
68 0	286	7,571	14 0	3 50	4 20	0 99	3 41
69 0	313	9,695	14 5	3 70	4 50	1 07	3 53
69 3	238	8,625	15 2	3 60	4 35	1 00	3 20
72 5	330	10,433	15 4	3 40	4 25	1 00	2 85
75 4	259	9,800	16 1	3 60	4 05	0 72	3 33
Females (Normal)							
45 7	10	2,380	11 1	2 75	3 20	0 84	2 70
48 8	12	2,885	11 7	2 90	3 30	0 72	3 05
49 3	10	3,640	11 7	3 50	3 60	0 85	3 00
50 0	29	3,220	12 5	3 00	3 80	0 85	2 90
50 2	3	3,050	11 5	3 00	3 60	0 80	2 78
50 4	10	2,900	11 4	3 10	3 65	1 04	2 73
51 8	10	3,230	11 6	3 10	3 50	0 77	2 95
52 5	40	3,850	13 7	3 45	3 50	0 84	3 05
52 7	66	3,925	12 4	2 81	3 45	0 87	2 71
53 1	35	3,783	12 6	2 90	3 30	0 72	3 00
53 1	32	3,630	11 5	2 20	3 72	0 81	3 11
55 2	36	3,769	13 0	3 00	3 71	1 13	2 85
55 4	47	3,945	12 1	3 30	3 85	0 87	3 25
55 6	60	4,645	12 4	3 10	3 90	0 97	2 95
56 1	63	5,215		3 05	3 65	0 84	3 23
56 3	158	5,475	13 2	3 32	4 40	0 90	3 18
56 3	68	5,144	12 8	3 20	3 65	0 82	2 82
57 3	51	5,600	12 5	3 30	4 00	0 91	3 28
57 5	91	5,130	13 0	3 40	4 00	0 97	3 30
57 9	83	5,157	14 2	3 20	4 00	0 94	3 10
58 2	82	5,606	13 4	3 00	3 70	0 97	3 05
58 5	85	6,105	12 4	3 50	4 10	0 92	2 97
58 7	83		12 3	3 30	3 90	0 90	3 20
59 0	75	5,016	12 5	3 10	3 92	0 97	3 02
59 5	143	6,350	12 6	3 32	3 90	0 91	3 43
60 3	99	5,820	12 2	3 30	4 20	1 11	3 43
60 5	79	4,663	14 1	3 05	3 90	1 11	2 85
60 8	106	5,298	13 0	3 65	4 10	0 96	2 28
61 0	152	6,255	14 8	3 25	4 00	0 90	3 10
61 1	90	4,990	12 7	3 30	4 00	0 91	3 25
61 7	134	5,490	13 8	3 35	3 55	0 89	3 15
61 8	162	6,350	13 8	3 70	4 40	1 07	3 28
61 9	109	6,090	14 4	3 20	3 87	0 97	3 44
62 0	68	5,405	13 5	3 40	4 25	1 09	3 05

compared according to crown-heel length in relation to days in age, using graphic methods. The curves of Richdorf's data drawn through the mean for each month is depicted in figure 9 for the males, and in

TABLE 8—*Table of Data—Continued*

Crown Heel Length, Cm	Age, Days	Weight, Gm	Fronto occipital Diameter, Cm	Widest Transverse Diameter of Palate, Cm	Actual Surface Width of Palate, Cm	Height of Palate, Cm	Length of Alveolar Process, Cm	
Females (Normal)—Continued								
62.7	115	6,600	14.0	3.00	4.00	1.13	3.25	
63.7	176	6,718	14.0	3.50	4.25	0.94	3.25	
64.4	259	7,125	15.2	3.40	4.10	1.00	3.25	
64.5	100	6,711	13.0	3.42	4.00	0.86	3.44	
64.8	203	8,210		3.21	3.70	0.74	3.20	
65.7	213	6,990	13.6	3.60	4.20	1.04	3.48	
66.9	241	7,520	14.4	3.40	3.92	1.08	3.25	
68.0	325	8,200	14.2	3.70	4.15	0.93	3.05	
68.2	188	7,199	14.9	3.20	3.90	0.88	3.40	
68.5	278	7,810	14.7	3.50	4.15	0.94	3.48	
69.1	283	8,130	13.7	3.60	4.40	1.06	3.55	
70.0	272	8,725	15.0	3.60	4.20	1.05	3.55	
70.2	238	7,965		3.22	4.00	1.00	3.35	
70.7	282	8,630	14.5	3.35	4.15	0.91	2.95	
71.5	344	8,190	15.8	3.55	4.35	1.11	3.60	
73.8	315	9,010	14.0	3.85	4.52	1.11	3.25	
75.5	362	10,020	14.7	3.75	4.55	1.11	3.26	
Crown Heel Length, Cm	Age, Days	Weight, Gm	Fronto occipital Diameter, Cm	Widest Transverse Diameter of Palate, Cm	Actual Surface Width of Palate, Cm	Height of Palate, Cm	Length of Alveolar Process, Cm	Width of Cleft, Cm
Males (Maldeveloped)								
47.5	11	2,815	11.1	3.70	3.10	1.26	3.30	1.79
50.0	10	3,325	12.5	4.20	3.20	1.23	2.75	1.79
50.3	3	2,990	11.4	3.80	3.90	1.17	3.00	1.40
50.9	58	6,278	12.2	3.60	3.70	1.21	3.00	1.09
51.4	42	3,765		4.00	3.20	1.24	3.05	1.20
51.6	16	3,210	11.7	3.70	3.60	1.20	2.95	0.96
51.7	47	4,260	12.6	4.10	4.30	1.54	2.95	0.93
52.0	47	3,729	12.0	4.20	3.55	1.26	3.20	1.35
52.1	28	3,325	12.7	3.60	3.40	1.11	2.75	1.41
52.3	25	3,500	11.1	3.70	3.80	1.18	3.10	1.35
52.7	46	3,480	12.6	3.90	3.60	1.33	2.88	1.42
53.6	40	3,670	13.4	3.70	3.90	1.17	3.10	1.09
56.8	56	4,309	12.5	3.45	3.70	1.18	3.30	0.96
56.9	121	4,500	12.7	4.10	3.50	1.05	3.40	1.34
56.9	21	4,280	12.3	4.10	3.70	1.17	2.85	1.26
57.0	71	4,585	13.7	3.90	4.10	1.26	3.13	1.38
57.8	89	3,645	13.6	3.30	3.90	1.04	3.00	
59.0	76	4,336	11.9	3.50	3.20	1.10	3.20	1.34
59.2	101	5,225	13.8	3.80	4.00	1.26	3.20	1.23
59.5	110	5,443	14.3	4.30	4.30	1.29	3.50	1.43
63.4	190	5,415	13.8	3.80	3.60	1.09	3.50	1.12
75.1	391	8,845	15.8	3.75	4.30	1.39	3.60	0.87
Females (Maldeveloped)								
52.2	41	3,033	12.5	3.50	3.75	1.17	3.10	1.10
52.8	71	3,645	12.3	3.60	3.70	1.20	2.85	1.59
58.9	81	3,825	13.1	3.70	3.90	1.16	3.20	1.20
59.7	95	4,705	13.0	3.50	4.00	1.26	2.85	1.07
63.7	246	5,355	12.8	3.60	4.20	1.27	3.30	0.78
66.1	186	5,897	13.0	4.20	4.10	1.09	3.20	1.39

figure 10 for the females. Three times the probable errors of the means is indicated in each figure. Field graphs of the length with age of the present study are included in each figure, a difference in symbol indicating whether normal or maldeveloped. The children of this series are seen to be slightly smaller than those collected by Richdorf, especially

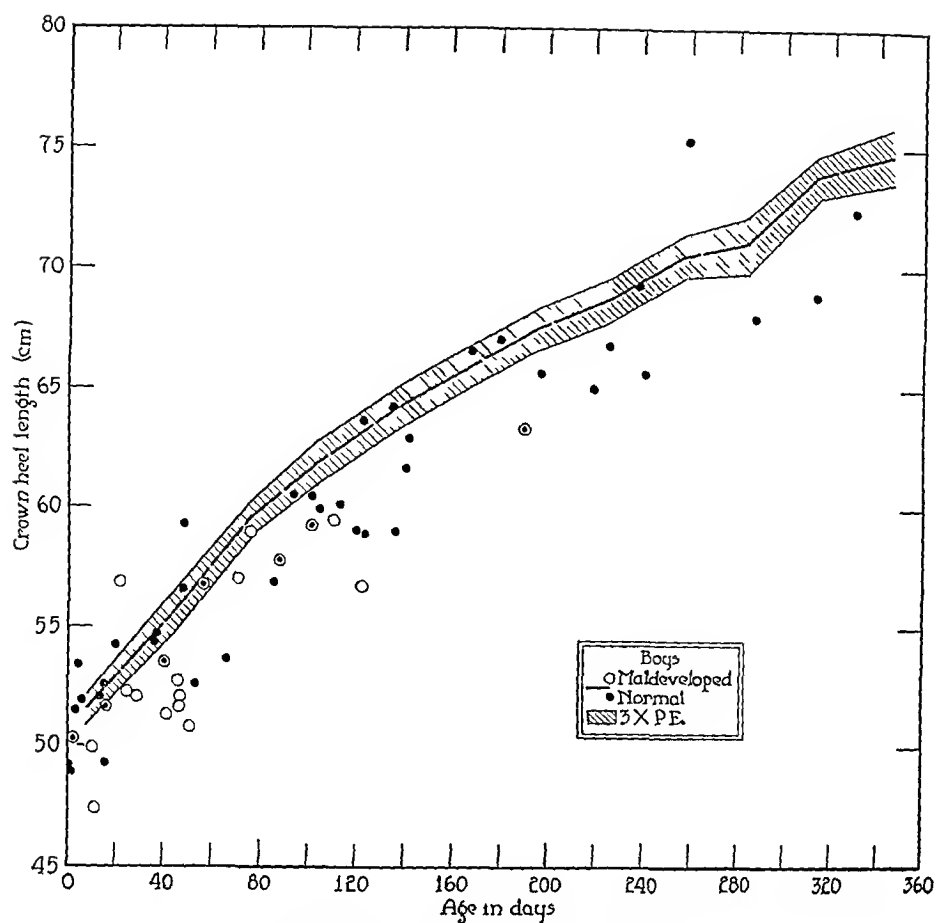


Fig 9—The curve of Richdorf's data for male children drawn through the mean for each month and field graphs of the length with age of the male children of the present study

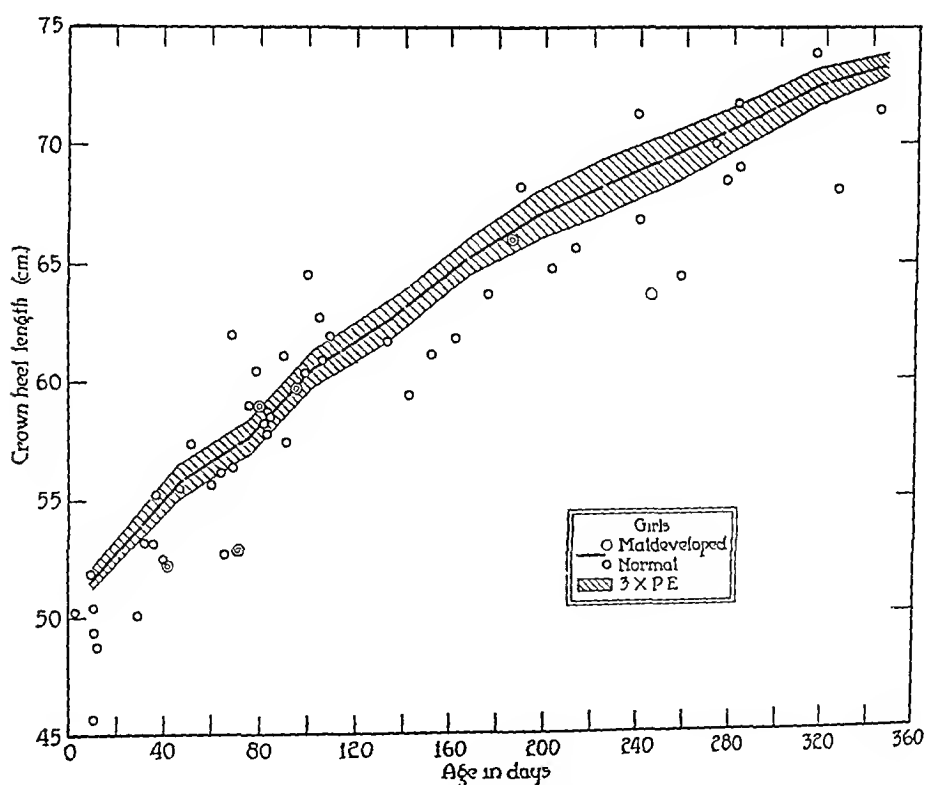


Fig 10—The curve of Richdorf's data for female children drawn through the mean for each month and field graphs of length with age for the female children of the present study

is this true of the male children. The maldeveloped children, however, are approximately the same length for age and sex as the normal children of this series.

The question then arose whether or not the difference in length of males and females for the same age necessitated treating them separately according to sex. In a series as small as this it would be advantageous to combine boys and girls. In the pathologic series the males predominate approximately as 4.5:1, but in the normal material the females predominate as 5:4. Although in infancy, the female is smaller than the male, her bodily proportions are approximately the same. If this general rule holds for these data, they could be analyzed without regard to sex. For instance, if males and females of the same length have the same sized heads, the sex differences in length for age could be eliminated by using length instead of age as a base. To test this supposition, the trends of the fronto-occipital diameter with length were fitted by the method of least squares for both the normal boys and girls. This is the general method used throughout this study.²

Field graphs of the fronto-occipital diameter of the head with body length and their fitted trend are depicted in figure 11. The measures for male and female children are depicted in separate graphs with

2 D = difference between calculated and observed value of Y

$$Y = BX + A$$

$$BX + A - Y = D$$

$$F = (BX + A - Y)^2 = \text{a minimum}$$

$$\text{Differentiating with respect to } B \quad \frac{DF}{DB} = \sum (BX + A - Y)X = 0$$

$$\text{Differentiating with respect to } A \quad \frac{DF}{DA} = \sum (BX + A - Y)1 = 0$$

Now solve the foregoing two simultaneous equations for B and A

$$(1) \sum X^2 B + \sum XA - \sum YX = 0$$

$$(2) \sum XB + \sum A - \sum Y = 0$$

$$(3) \sum XY = \sum X^2 B + \sum XA$$

From (2) since $\sum A = NA$ where

$$(4) \sum Y = \sum XB + NA$$

N = number of observations

$$\text{Multiply (3) by } \frac{1}{\sum X}$$

$$(5) \frac{\sum XY}{\sum X} = \frac{\sum XB}{\sum X} + A$$

$$\text{Multiply (4) by } \frac{1}{N}$$

$$(6) \frac{\sum Y}{N} = \frac{\sum XB}{N} + A$$

Subtracting to solve for B

$$\frac{\sum XY}{\sum X} - \frac{\sum Y}{N} = \frac{\sum XB}{\sum X} + A - \frac{\sum XB}{N} - A$$

$$\frac{\sum XY}{\sum X} - \frac{\sum Y}{N} = B \left[\frac{\sum X}{\sum X} - \frac{\sum X}{N} \right]$$

$$B = \frac{\frac{\sum XY}{\sum X} - \frac{\sum Y}{N}}{\frac{\sum X}{\sum X} - \frac{\sum X}{N}}$$

From (6)

$$A = \frac{\sum Y}{N} - \frac{\sum XP}{N}$$

their respective straight line trends. For the purpose of comparison the fitted trends of the data for females and males are depicted in figure 25. The trends for both sexes practically coincide, demonstrating no essential sex differences in the size of the head. For this reason, most of the comparisons of maldeveloped cases with the normal have been made without regard to sex.

DIVISION OF DATA

The data for normal and abnormal material have each been divided according to sex for further comparisons in the study of certain dimensions of the palate, namely, the widest transverse diameter of the

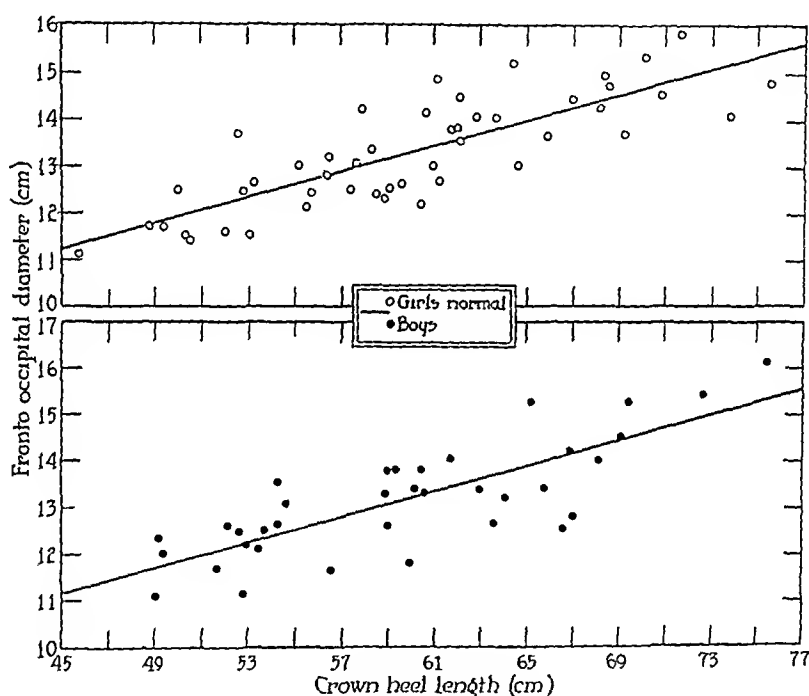


Fig 11—Field graphs and trend of the fronto-occipital diameter with body length of the female and male children of this study

palate, actual surface width of the palate and height of the palate. After these various divisions of the material were made, a straight line was fitted to the measurements of each group by the method of least squares. The root mean square or standard deviation, probable error, and the probable error of the trend were computed for each group.³ The result of these computations are recorded in table 9.

$$3 \text{ Standard deviation } \sigma = \sqrt{\frac{\sum \Delta^2}{N}}$$

$$\text{Probable error } P E = 0.6745 \sigma$$

Bowley Elements of Statistics, ed 4, London, P. S. King & Son, 1920, p. 270

$$\text{Probable error of the trend } P E T = \frac{P E}{\sqrt{N}}$$

Kelley Statistical Method, New York, The Macmillan Company, 1923, p. 105

TABLE 9—*Table of Formulas*

Dimension	Data Included	Num ber of Obser va tions	Formula	Root Mean Square Devia tion, Cm	P I	P E m	Average Devia tion	Aver age per Cent Devia tion
Fronto occipital diameter	Combined male, female (normal)	86	$y = 5.067 + 0.136 L$	0.677	0.457	0.049	0.553	4.06
	Combined male, female (malde veloped)	27	$y = 5.495 + 0.129 L$	0.641	0.432	0.083	0.537	4.50
	Male (normal)	38	$y = 4.958 + 0.137 L$	0.692	0.467	0.075	0.565	3.64
	Female (normal)	48	$y = 5.106 + 0.116 L$	0.662	0.447	0.065	0.550	4.12
Widest transverse diameter of palate	Combined male, female (normal)	91	$y = 2.025 + 0.022 L$	0.181	0.122	0.013	0.148	4.48
	Combined male, female (malde veloped)	28	$y = 3.799 - 0.0001 L$	0.260	0.168	0.032	0.214	5.64
	Male (normal)	40	$y = 2.216 + 0.020 L$	0.146	0.098	0.016	0.117	3.43
	Female (normal)	51	$y = 1.787 + 0.025 L$	0.183	0.123	0.017	0.142	4.33
	Male (maldevel oped)	22	$y = 4.100 - 0.005 L$	0.263	0.177	0.038	0.210	5.50
	Female (malde veloped)	6	$y = 1.857 + 0.031 L$	0.197	0.128	0.052	0.148	3.94
Actual surface width of palate	Combined male female (normal)	91	$y = 2.181 + 0.030 L$	0.205	0.138	0.015	0.165	4.17
	Combined male, female (malde veloped)	28	$y = 1.905 + 0.033 L$	0.282	0.190	0.036	0.218	5.85
	Male (normal)	40	$y = 2.483 + 0.026 L$	0.197	0.133	0.021	0.166	4.12
	Female (normal)	51	$y = 1.829 + 0.035 L$	0.193	0.130	0.018	0.150	3.84
	Male (maldevel oped)	22	$y = 2.157 + 0.028 L$	0.320	0.216	0.046	0.250	6.76
	Female (malde veloped)	6	$y = 2.116 + 0.031 L$	0.067	0.045	0.018	0.073	1.34
Height of palate	Combined male, female (normal)	91	$y = 0.570 + 0.006 L$	0.101	0.068	0.007	0.079	1.44
	Combined male, female (malde veloped)	28	$y = 1.221 - 0.0002 L$	0.100	0.068	0.013	0.073	6.02
	Male (normal)	40	$y = 0.672 + 0.004 L$	0.105	0.071	0.011	0.085	0.93
	Female (normal)	51	$y = 0.403 + 0.009 L$	0.093	0.063	0.009	0.073	7.55
	Male (maldevel oped)	22	$y = 1.176 + 0.0007 L$	0.114	0.077	0.016	0.083	6.80
	Female (malde veloped)	6	$y = 1.310 - 0.002 L$	0.068	0.046	0.019	0.053	4.49
Length of alveolar process	Combined male, female (normal)	91	$y = 2.015 + 0.019 L$	0.179	0.121	0.013	0.145	4.61
	Combined male, female (malde veloped)	28	$y = 1.824 + 0.023 L$	0.176	0.114	0.022	0.135	4.76
Width of cleft	Combined male female	27	$y = 2.622 - 0.018 L$	0.222	0.150	0.029	0.177	13.80

ANALYSIS OF THE DIFFERENCE BETWEEN NORMAL AND
CLEFT PALATES

The measurements of the normal child and the abnormal child were graphically compared. The method was similar for each set of dimensions. A field graph of the palate measurements of the normal children with body length is presented with their fitted trend and three times its probable error. Field graphs of the measurements of the abnormal children with body length is also presented with their fitted trend and three times its probable error. For purposes of comparison, the fitted trends of the normal and abnormal children are depicted in figure 25 in their actual relation to each other.

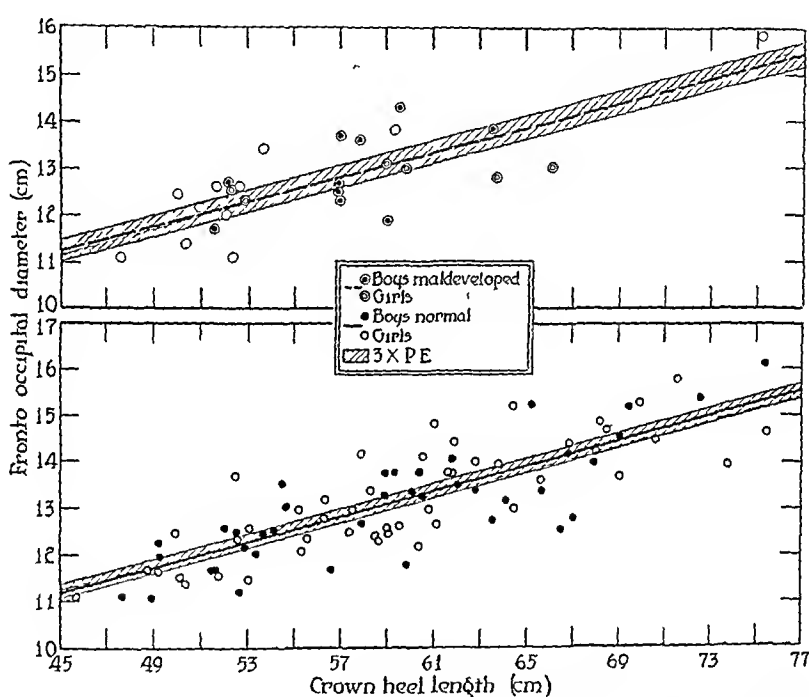


Fig 12—Field graphs of the fronto-occipital diameter with body length for the abnormal children and for the normal children. The fitted trend and three times the probable error is indicated in each graph.

Fronto-Occipital Diameter—The fronto-occipital diameter of the normal children is compared with the same dimensions of the maldeveloped children in figure 12. A field graph of the fronto-occipital diameter of the normal children with body length is presented with their fitted trend and three times its probable error. A field graph of the fronto-occipital diameter of the abnormal children with body length is also presented with its fitted trend (indicated in broken line) and three times its probable error. For the purpose of comparison, the fitted trends of the normal and abnormal children are depicted in

figure 25 It is evident that there is no significant difference in the fronto-occipital diameter in these two groups, their trend falling well within the range of three times the probable error The size of the head is therefore approximately the same for the normal, as for the maldeveloped material

Surface Width of the Palate—The surface width of the normal palate is compared with that of the cleft palate in figure 13 Field graphs of both the normal and maldeveloped children are depicted The range of three times the probable error of the trend is indicated in each field graph For the purpose of comparison, the lines of trend for both groups of data are depicted in figure 25 Growth is definitely indicated, but it is doubtful if there is a significant difference in the surface width of the palate in the normal and maldeveloped children An increment is demonstrated of approximately 8 mm in the surface

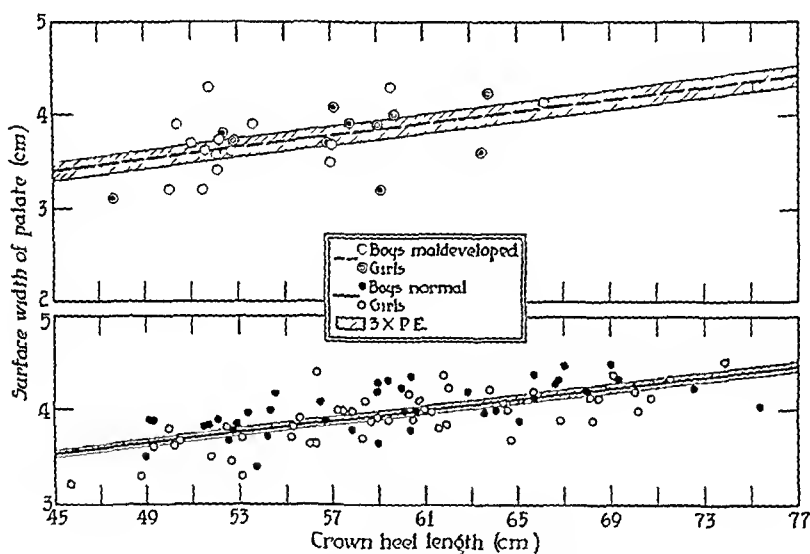


Fig 13—Field graphs of the surface width of the palate with body length for the abnormal children and the normal children The fitted trend and three times the probable error is indicated in each graph

width of the normal palate during that portion of the growth period included in this study, and a very similar amount of growth in the cleft palate The fitted line of trend for the maldeveloped material for 51 cm length is approximately 13 mm less than that for the normal material and at 59 cm length it is 1 mm less The foregoing points 51 and 59 cm, are chosen because the majority of the maldeveloped material is included within this length This apparent difference in surface width is probably not significant It may be due to greater difficulty in getting the end-point of measurement at the medial edge

of the cleft palate, or it may be the result of chance selection in the small group of the maldeveloped children. That chance selection is a cause for this difference is supported by analysis of the same data when divided according to sex. Field graphs of the data for males and

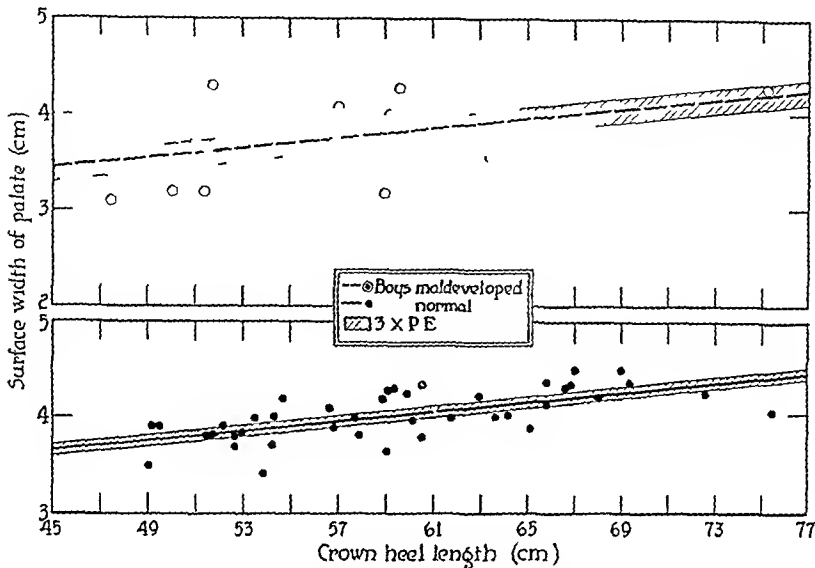


Fig 14—Field graphs of the surface width of the palate with body length for the abnormal and normal boys of this series. The fitted trend and three times the probable error is indicated in each graph.

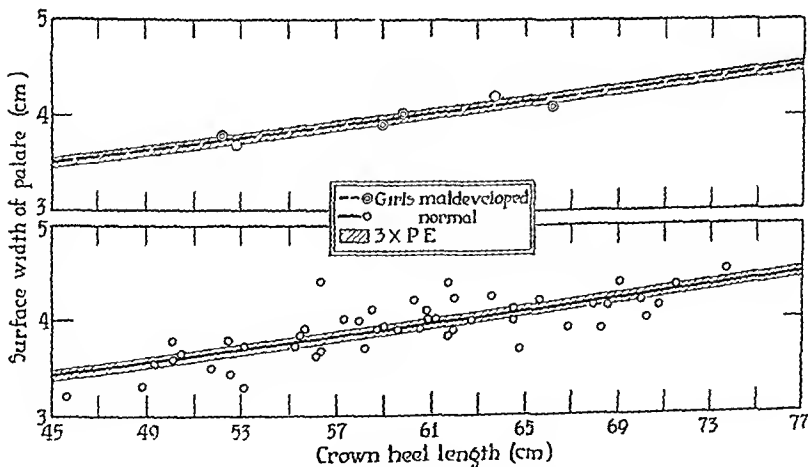


Fig 15—Field graphs of the surface width of the palate with body length for the abnormal and normal girls of this series. The fitted trend for each group of data and three times the probable error is indicated in each graph.

females are depicted in figures 14 and 15, respectively. Their lines of trend and the range of three times the probable error are indicated. For the purpose of comparison, the line of trend of each group of normal

data is depicted in figure 25 in its actual relation to the fitted trend of the abnormal material of the same sex. The fitted trend of the abnormal male children at 51 cm length is approximately 2.5 mm below that of the normal male children and at 59 cm length it is approximately 2 mm below that of the normal children, while on the other hand, the fitted trend of the maldeveloped females indicates a wider actual surface width in the cleft than in the normal palate.

Widest Transverse Diameter of the Palate—The widest transverse diameter of the palate is depicted in figure 16, in which field graphs of the normal children and the maldeveloped children are presented with the trend for each group of data. Three times the probable error of the

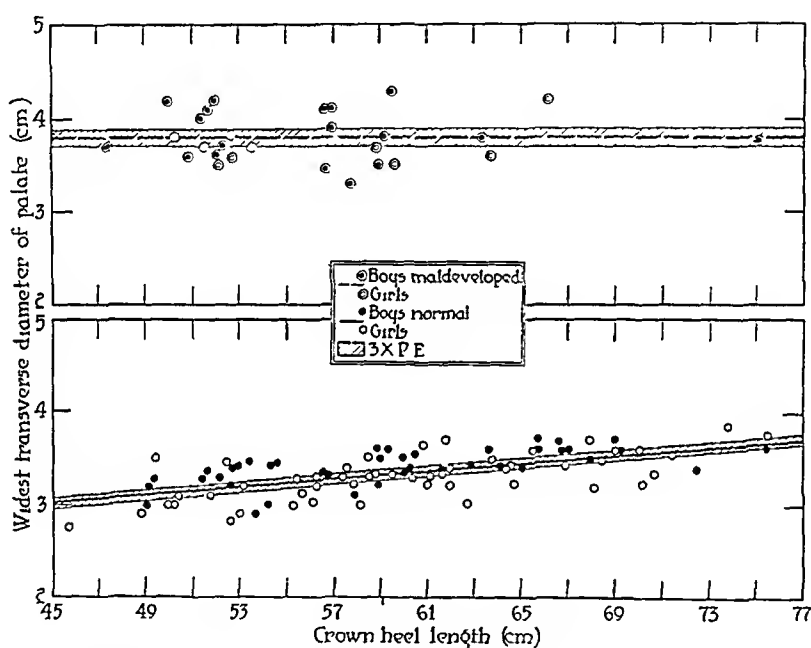


Fig 16—Field graphs of the widest transverse diameter of the palate with body length for the abnormal and normal children of this series. The fitted trend and three times the probable error is indicated in each graph.

fitted trend is indicated in each field graph. For the purpose of comparison, the fitted trend of each group of data is depicted in figure 25. Definite growth and also significant difference in the widest transverse diameter between the normal and the cleft palate is indicated. Approximately 6 mm increase in width of the normal palate during the period of growth included in this study is demonstrated but no increase in the width of the cleft palate. Since the fitted line of trend for the cleft palate shows no spread or increase of the width of the maxillae during the period included in this study, therefore, if this material is representative any growth which does occur is toward the midline. This would

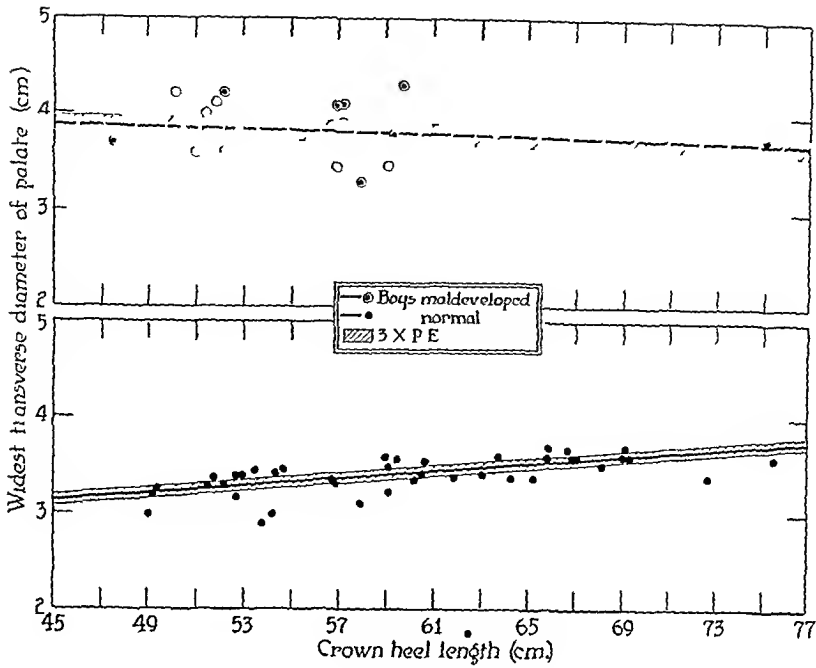


Fig 17—Field graphs of the widest transverse diameter of the palate with body length for the abnormal and normal male children. The fitted trend and three times the probable error is indicated.

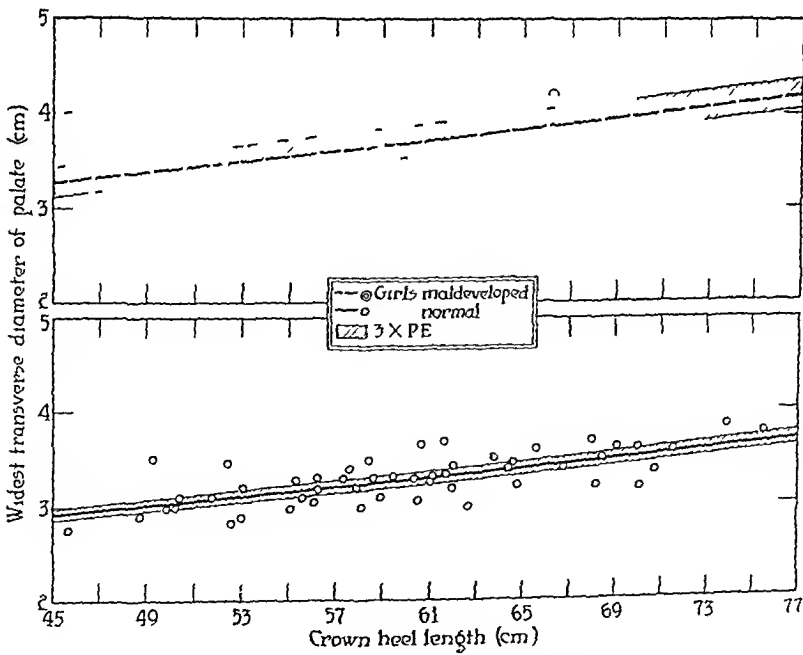


Fig 18—Field graphs of the widest transverse diameter of the palate with body length for the abnormal and normal female children. The fitted trend and three times the probable error is indicated in each graph.

lead one to expect that the cleft would become narrower as growth occurred in the palate. To check this, the width of the cleft was measured, and analysis of these measurements confirmed this supposition (fig. 23). This is the most unexpected and remarkable observation demonstrated in this study. That the transverse diameter of the cleft palate is greater than the transverse diameter of the palate of the normal child of equal body length is evident. The difference in width at the 51 and 59 cm lengths is approximately 7 and 5 mm, respectively. With the data grouped according to sex, field graphs and their trend for measures of the widest transverse diameter of the cleft and normal palate are depicted in figures 17 and 18 for male and female children respectively. For the purpose of comparison, the line of trend for the measures of male children normal and abnormal, are depicted in

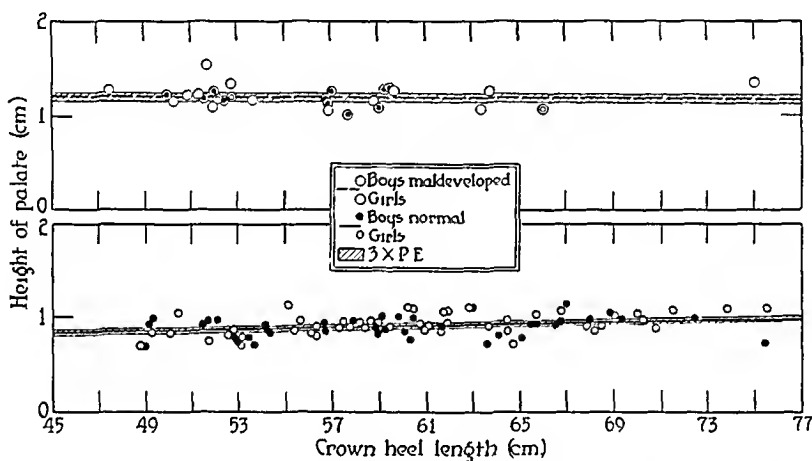


Fig. 19—Field graphs of the height of the palate with body length for the abnormal and normal children of this series. The fitted trend and three times the probable error is indicated in each graph.

figure 25 in their actual relation to each other, and the lines of trend for the measures of the female children are also depicted in similar manner in figure 25. As a whole, the results are similar to those in which no division as to sex was made.

Height of Palate—Comparison of the height of the palate is depicted in figure 19 which is composed of field graphs and their trends for the measures of normal children and the maldeveloped children. Three times the probable error of the trends is indicated in each field graph. For the purpose of comparison the trends of each group is depicted in figure 25. There is little increase in height during the period studied, approximately 1 mm for the normal palate and no increase for the cleft palate. That the cleft palate is definitely higher than the normal palate of children of the same body length, is demonstrated. At 51 cm crown-

heel length, the trend for the maldeveloped material is approximately 3 mm higher and at 59 cm length 2.5 mm higher. With the data grouped according to sex, field graphs and their trend for measures of the height of the normal palate and the cleft palate are depicted in figures 20 and 21 for the males and females, respectively. Three times

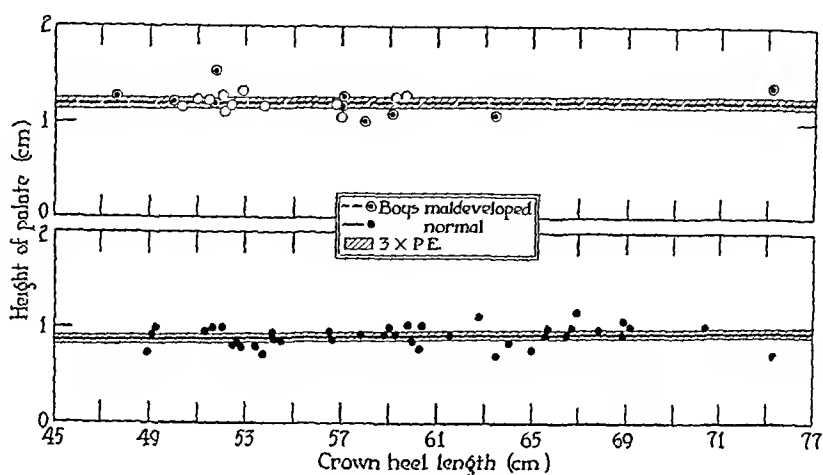


Fig 20—Field graphs of the height of the palate with body length for the abnormal and normal male children. The fitted trend and three times the probable error is indicated in each graph.

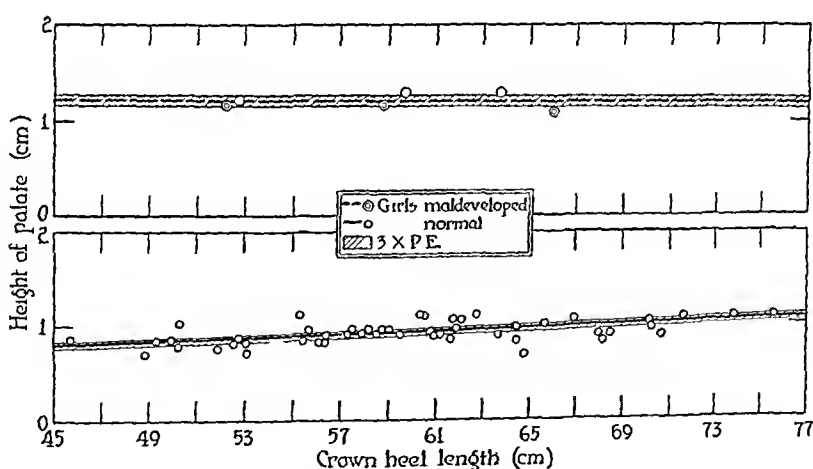


Fig 21—Field graphs of the height of the palate with body length for the abnormal and normal female children. The fitted trend and three times the probable error is indicated in each graph.

the probable error of the fitted trends for each group is depicted. For the purpose of comparison, the lines of trend for measures of the male children, normal and abnormal, are depicted in figure 25 in their actual relation to each other, and the lines of trend for measures of the female

children are also depicted in similar manner in figure 25. In general, the result is similar to that for the combined data.

Length of the Alveolar Process—The values determined for length of the alveolar process in the maldeveloped children were divided into three groups: the long side, the short side and the average of both sides in a case of bilateral cleft. There were twenty in each of the first two groups and eight in the latter. The arithmetical mean of each of these groups of dimensions was taken. For the long side it was 3.05 cm, for the short side, 3.11 cm, and 3.08 cm for the average length of the bilateral cleft palates. This reveals a discrepancy of less than 1 mm, which is within the possible error of measurement.

The length of the alveolar process of the palate is depicted in figure 22, which consists of field graphs and their line of trend for the

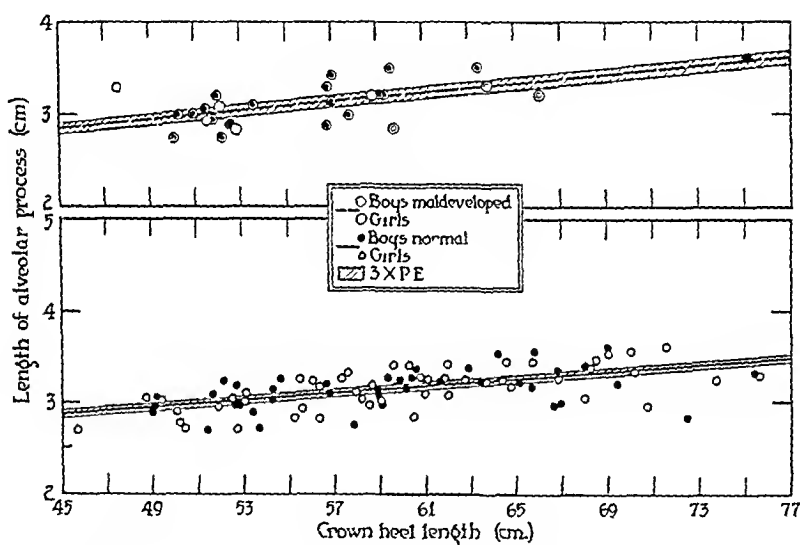


Fig. 22—Field graphs of the length of the alveolar process with body length for the abnormal and normal children. The fitted trend and three times the probable error is indicated in each graph.

measures of the normal children and the maldeveloped children. Three times the probable error of the fitted trends is indicated in each field graph. For the purpose of comparison the lines of trend of each group of data is depicted in figure 25.

Growth in length of the alveolar arc of the normal palate is approximately 5 mm during the period included in these data and as much, if not slightly more in the alveolar arc of the cleft palate.

Although on the whole in the maldeveloped children the fitted trend for length of the alveolar process with body length is slightly above that of normal children it does not appear to be a significant difference. In that portion of the graph which includes most of the

maldeveloped material, namely, from 51 to 59 cm crown-heel length, it is not greater than 0.5 mm. It is possible that some of this difference in length is due to the difference in the method of obtaining these dimensions. The normal palate was measured directly as the chord of the arc of one side of the alveolar process. The maldeveloped palate was measured for the most part as two segments or chords, the sum of whose circumference represented the entire alveolar arc, that is, the arc of the maxillary portion of the alveolar border and one-half the premaxilla were summated to obtain the length of the alveolar arc. Since the sum of two chords is greater than the chord of the sum of the circumference they represent, this probably is a slight source of error in the direction indicated by the lines of trend.

Width of the Cleft—Since analysis of the widest transverse diameter of the palate demonstrated an increase of approximately

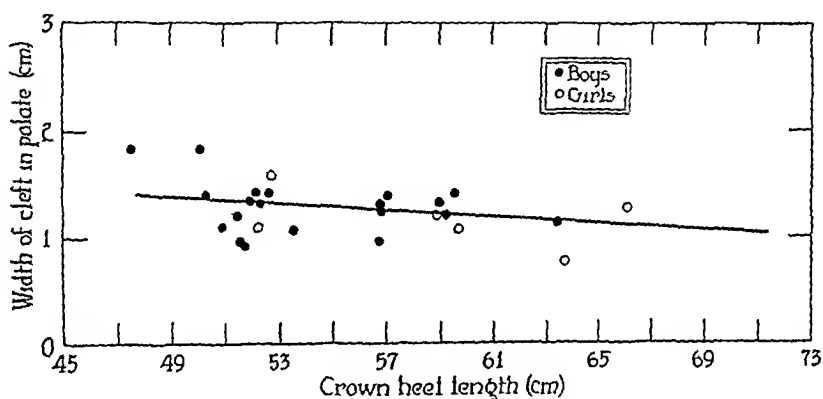


Fig. 23—A field graph of the width of the cleft with body length. The fitted trend is indicated.

7 mm in the first year and no increase in the same dimension of the cleft palate during this same period, although there was growth in the palate of both the normal and abnormal children, as demonstrated by the actual surface measurement, it should follow that the cleft becomes smaller or more narrow during the period of growth included in this investigation. This supposition is supported by analysis of measures of the cleft. A field graph of the width of the cleft and its line of trend is depicted in figure 23. Between the extreme ends of the graph it diminishes approximately 4 mm. The material is so variable that this may be a chance selection of wide clefts in the smaller specimens, but since it checks so well with the other observations it is more probable that there is actual growth of the tissues toward the midline. This can be checked by repeated measurements on the same child over a period of several months.

COMMENT

Comparison of the results of this investigation with the dimensions of the palate, as determined by other investigators, cannot be accurately made, since their results have not been analyzed in this manner, the age distribution of material does not correspond, and the method of taking and the end-points of measurements are not the same. In general, however, there is a similarity of results. In table 10 are recorded the results of investigators quoted in the section on literature and included are those of this investigation for comparison.

Congenital malformations of the upper lip and palates are most common in boys. Haug reported that in 2,352 instances of such maldevelopment the male was effected in 64.3 per cent. Davis reported 24 children with clefts, 71 per cent of whom were boys. In this series there were 20 boys and 6 girls, or 77 per cent males and 23 per cent females.

TABLE 10.—*Dimensions of the Palate Compared with Results of Other Investigators*

Investigator	Dimension		
	Width, Cm	Height, Cm	Length Cm
Alkan (average)	2.70	1.20	3.20
Denzer (average)	3.09	0.88	
Franke (average)			2.65
This study (median)	3.30	0.95	3.15

Congenital clefts of the upper lip and upper part of the face are most common on the left side. Haug reported 2,238 cases with left-sided cleft in 50.9 per cent, right-sided in 21.8 per cent and bilateral in 27.3 per cent. In general, only complete clefts are included in the series of this investigation and are not entirely comparable, therefore, with this report of Haug where all clefts were included. This may be the reason in part for the difference in frequency in this series, namely, left-sided cleft, 38 per cent, right-sided cleft, 35 per cent and bilateral cleft, 27 per cent.

The results of this investigation would, of course, have been more conclusive if the maldeveloped material was represented by a larger series. Anomalies of the upper part of the face and jaw are not of frequent occurrence. They occur in colored people once in 1,788 births and in white people once in 915 births, according to the figures of Davis who reviewed the birth records of 28,085 consecutive deliveries in which there occurred 24 instances of cleft. Frobchus in 1865 reported 76 instances of cleft in 180,000 hospital admissions or approximately

1 to every 2,400 Since complete clefts, unilateral or bilateral, were chosen for the present study, many cases with lesser degrees of cleft were rejected Complete clefts, unilateral or bilateral, occurred in 73.4 per cent of 1,887 cases of clefts of the lip and palate reported by Haug, 24 per cent of which were complete bilateral clefts of the lip, process and palate

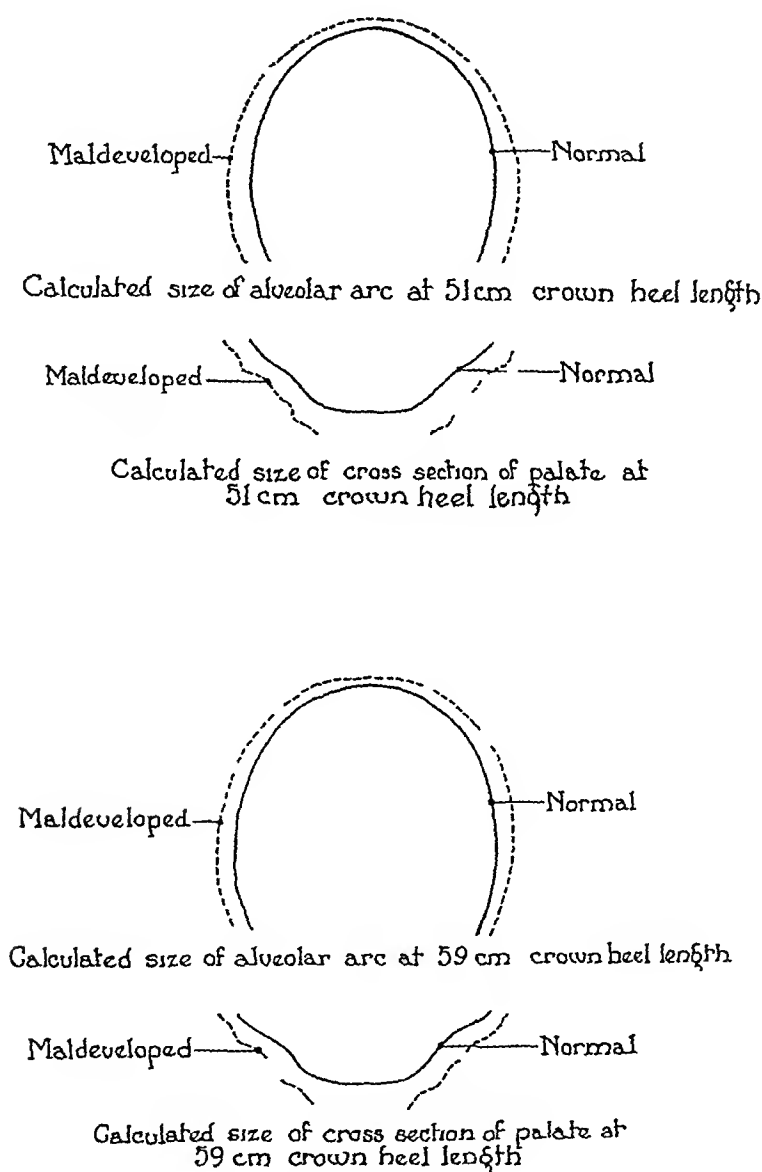


Fig 24—An outline of the alveolar process and a cross-section of the palate depicting, as determined in this study, the relative size of the abnormal and normal palate at 51 cm crown-heel length and 59 cm crown-heel length

Other problems in connection with surgical measures on maldevelopments of the upper lip and palate could be solved by this method, especially should the anatomic results of operations be investigated

SUMMARY

Growth increments of the normal palate during approximately the first year (from 49 to 75 cm crown-heel length) are as follows

Widest transverse diameter of palate	5.5 mm
Actual surface width of palate	8.0 mm
Height of palate	1.0 mm
Length of alveolar process	5.0 mm

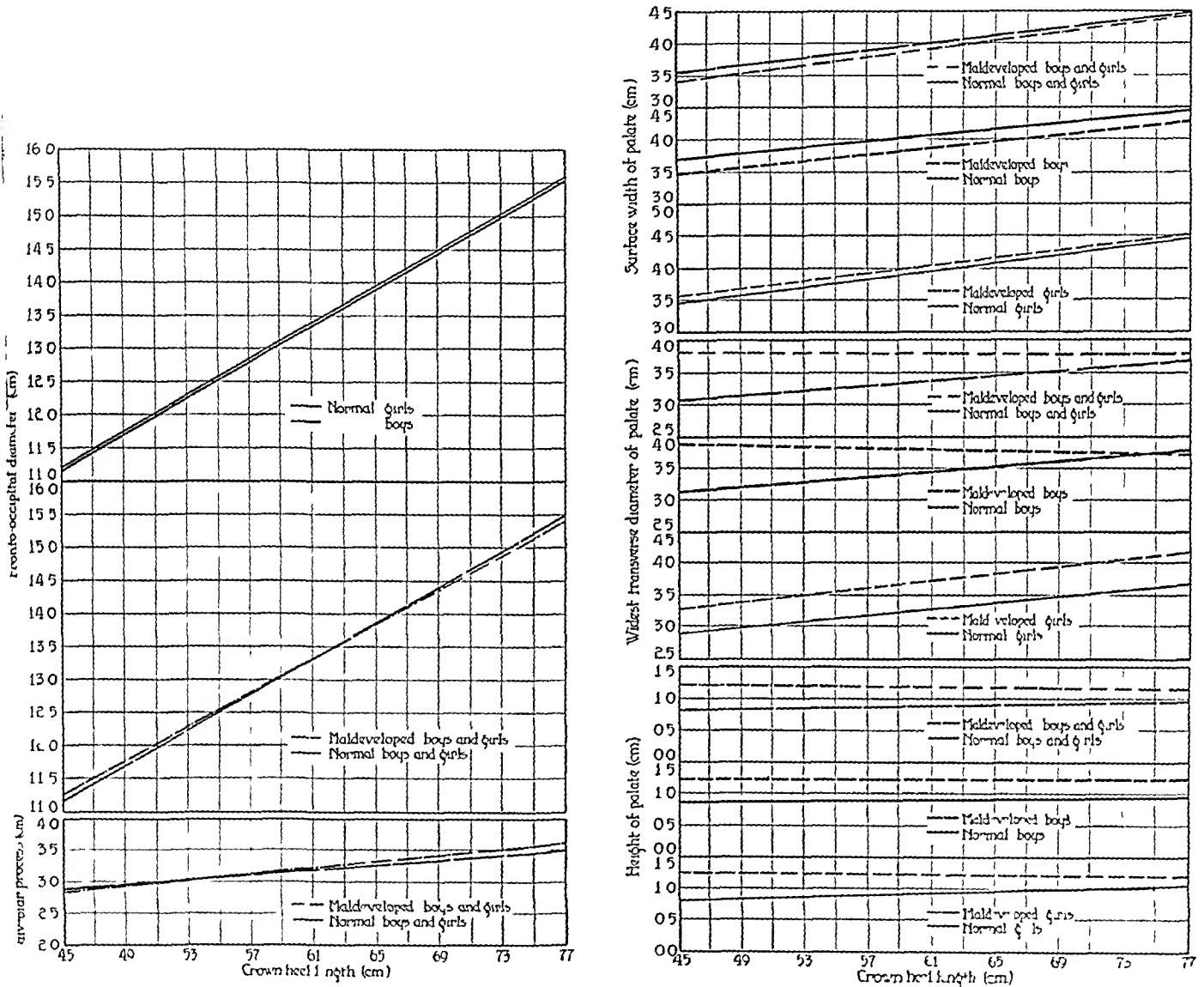


Fig 25—This figure illustrates the relation of the trends of (a) the surface width of the palate with body length, (b) the widest transverse diameter of the palate with body length, (c) the height of the palate with body length, (d) the frontal-occipital diameter of the head with body length, and (e) the length of the alveolar process of the palate with body length

Dimensions of cleft palate except surface width are larger than those of the normal palate. The cleft palate dimensions compared with those

of the normal palate for children of 51 and 59 cm crown-heel length, respectively, are as follows

	51 cm crown- heel length, mm	59 cm crown- heel length, mm
Widest transverse diameter of palate	+70	+50
Actual surface width of palate	—13	—10
Height of palate	+30	+25
Length of alveolar process	00	+05

These differences in the size of the cleft palate and the normal palate are graphically represented in figure 24

The width of the cleft was found to diminish 15 mm during the growth interval between 51 and 59 cm crown-heel length. This was to be expected, after it was found that the widest transverse diameter during the same interval remained approximately unchanged

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HISTOLOGIC STUDIES OF THE BRAIN IN CASES OF FATAL INJURY TO THE HEAD

I PRELIMINARY REPORT *

CARL W RAND, M D

LOS ANGELES

Perhaps one of the most obvious gross changes found in the brain following a severe injury to the head is an increase in its fluid content. This is commonly referred to as cerebral edema. At autopsy the brain appears swollen, and under certain circumstances it is probably actually heavier than normal. The increase in fluid, as judged by gross appearance, is general in distribution. It is not confined to the substance of the brain alone, although this tissue may be wetter than normal, in addition, there is often an excess of fluid in the subarachnoid space and in the ventricular system. This excess of cerebrospinal fluid may be demonstrated clinically. At lumbar puncture the pressure of the fluid is usually increased, the rapidity of its flow is quickened, and the actual amount that may be withdrawn is often considerably greater than normal. The presence of a "wet" edematous brain is often seen at operation. The pathologic and physiologic changes underlying this increase in fluid content have not been sufficiently explained. The studies that will be briefly outlined in this report are being conducted for the purpose of investigating the sources of this fluid, as well as the reason for its increase.

The first inquiry was directed to a study of the choroid plexus. It seemed reasonable to assume that the activity of this structure might be altered by trauma. If so, this might lead to morphologic changes that could be seen under the microscope. Other considerations, however, soon presented themselves for investigation, and finally led to a histologic survey of more distant portions of the brain.

It was sought to ascertain the condition of the ependymal lining of the ventricles and its possible rôle as an accessory source of cerebrospinal fluid, to study the changes that might occur in the neurons or glial cells proper, to examine the condition of the leptomeninges, in seeking an explanation of the so-called "wet or sweaty" brain, to investigate the condition of the substance of the brain, especially with reference to possible enlargement of the perivascular and pericellular spaces, and to attempt experimentally to determine whether fluid seeps through the semipermeable membranes of the small capillary walls into the perivascular and hence into the pericellular spaces.

* Submitted for publication, July 26, 1930

Abundant material has been placed at our disposal through the kindness of Dr A F Wagner of the coroner's department We have chosen sixty-one pathologic brains for study, using ten normal brains as controls Dr Cyril B Courville has been working on other phases of this study, and more detailed reports will be presented with him later

HISTORICAL DATA

Weed¹ (1922) has given an excellent review of the generally accepted present conception of the sources and circulation of cerebrospinal fluid The supposition that this fluid is secreted by the choroid plexuses is usually ascribed to Faivre² (1853) and Luschka³ (1855) Faivre was the first to describe the glandular histologic structure of the choroid plexus He demonstrated that the villous projections were covered by epithelial cells which he believed showed indications of secretory activity Luschka originated the hypothesis "that the choroid plexuses elaborate the greater portion of the cerebrospinal fluid" and was the first to show hyalin-like inclusions in the cells These may have been vacuoles His hypothesis has been widely accepted, although conclusive proof that the choroid plexus is a secretory gland has never been actually established Findlay⁴ (1899) made the most careful study of the choroid plexus up to his time He described the glandular structures of the cells and called attention to the pigmented globules and vacuoles in them He concluded that "there is a constant change going on in the epithelial cells and they normally undergo a process of vacuolation and rupture to form the choroid plexus secretion" Studnicka⁵ (1900) found similar evidence of secretion both in the cells of the choroid plexus and in the ependymal cells in certain areas Pettit and Girard⁶ (1902) described hyalin-like globules in the choroidal epithelium of animals, but thought that these did not represent secretory vacuoles Loeper⁷ (1904) studied the choroid plexus in man and described pigmented granules in the cells He also found pigmented granules within the vacuoles by using osmic acid preparations and concluded that the

1 Weed L H The Cerebrospinal Fluid, *Physiol Rev* **2** 171 (April) 1922

2 Faivre E Des granulations meningiennes, *These de Paris* 1853

3 Luschka, H Die Adergeflechte des menschlichen Gehirns, Berlin, 1855

4 Findlay J W The Choroid Plexuses of the Lateral Ventricles of the Brain Their Histology Normal and Pathological *Brain* **22** 161 1899

5 Studnicka F K Untersuchungen über den Bau des Ependyms der nervösen Centralorgane *Anat Hefte* **15** 303 1900

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7 Loeper M Sur quelques points d'histologie normale et pathologique des plexus choroides de l'homme *Compt rend Soc de biol* **56** 1010 1904

choioid plexus was a glandular organ. From histochemical investigation Yoshimura⁸ (1910) concluded that the secretion of cerebrospinal fluid by the choioid plexus "was related to the aggregation of the smaller cytoplasmic granules together into large vacuoles for discharge." Pelizzzi⁹ (1911) felt that the epithelial cells of the plexus secreted granules which increased in size by the absorption of fluid plasma until they were extruded.

More convincing evidence of this secretory nature of the choioid plexus has been established by physiologic and pharmacologic methods than by purely anatomic and histologic observations. Cappelletti¹⁰ (1900) found that ether and pilocarpine increased the flow of spinal fluid, while atropine and hyoscyamine decreased it. Pettit and Guard¹¹ repeated his work, with similar observations. In addition, they made histologic studies of the choioid plexus and found an actual increase in the size of the choioidal epithelium. They described these cells as being practically doubled in height while under activity. They also noted a granular zone near the base of the cells and a clear, sometimes vesicular zone near the apex, which they concluded indicated that the choioid plexus possessed a secretory activity. Meek¹¹ (1907) repeated their experiments coming to identical conclusions, and stated that "the two things most striking about these modified cells are their great increase in height and the appearance of so much clear space at the distal side of the nucleus." Claisse and Levy¹² (1897) described hypertrophy of the choioid plexus in a case of internal hydrocephalus. Dandy and Blackfan¹³ (1913) and Frazier and Peet¹⁴ (1914) produced internal hydrocephalus experimentally by occlusion of the aqueduct of Sylvius. In 1919 Dandy¹⁵ again produced unilateral hydrocephalus by obstructing one foramen of Monro in which the choioid plexus was left intact in

8 Yoshimura, K. Das histochemische Verhalten des menschlichen Plexus chorioidens, Arb. a. d. neurol. Inst. a. d. Wien Univ. **18** 1, 1910.

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15 Dandy, W. E. Experimental Hydrocephalus, Ann. Surg. **70** 129 (Aug.) 1919.

the obstructed ventricle. When he removed the choroid plexus of the ventricle before obstructing the foramen of Monro, internal hydrocephalus did not occur. His experiments furnish the strongest evidence to prove that the choroid plexuses elaborate cerebrospinal fluid. Cushing¹⁶ (1914), while operating on a child with a porencephalic cyst observed exudation of a clear fluid from the surface of the choroid plexus. Becht¹⁷ (1920) on the other hand in a critical review not only questioned whether the choroid plexus secretes cerebrospinal fluid but has also challenged the generally accepted theories of the circulation and absorption of this fluid as outlined by practically all other observers. However, he offered no adequate explanation as to the source or pathways of absorption of the fluid. Wislocki and Putnam¹⁸ (1921) demonstrated that granules of potassium ferrocyanide penetrated the ependymal cells lining the ventricles, but did not pass through the choroidal epithelium, in cases of experimental internal hydrocephalus in which the solution was introduced into the subarachnoid spaces. Nañagas¹⁹ (1921) demonstrated an increased intraventricular accumulation of fluid after intravenous injection of hypertonic salt solution but in no case found apparent absorption of the fluid by the cells of the choroid plexus.

Weed²⁰ (1914), in discussing the dual source of cerebrospinal fluid hypothesized that aside from the choroid plexus "the perivascular spaces also pour a certain amount of fluid into the subarachnoid space where this fluid mixes with the liquid produced in the cerebral ventricles." He failed to tell how the fluid gets into the perivascular spaces. He was of the opinion that "the ependymal cells lining the cerebral ventricles and central canal of the spinal cord may also contribute even in the adult a minimal addition to the intraventricular cerebrospinal fluid." Halliburton²¹ (1916) referred to the cerebrospinal fluid as serving as the lymph of the brain although he differentiated it from the true lymph as seen in lymphatic vessels. It is generally conceded that true lymphatic vessels do not exist in the dura mater of the brain. Sabin²² (1915-1916) pointed out that the use of the term "lymph" should be restricted to the fluid confined to true lymphatic vessels and should not be used to design-

16 Cushing H. Studies on Cerebro-Spinal Fluid, *J. M. Research* **31** 1 1914

17 Becht, F. C. Studies on Cerebrospinal Fluid, *Am. J. Physiol.* **51** 1 1920

18 Wislocki, G. B., and Putnam T. J. Absorption from Ventricles in Experimentally Produced Internal Hydrocephalus. *Am. J. Anat.* **29** 313 1921

19 Nañagas J. C. Experimental Studies on Hydrocephalus. *Bull. Johns Hopkins Hosp.* **32** 381, 1921

20 Weed L. H. Studies on Cerebrospinal Fluid. IV. The Dual Source of Cerebrospinal Fluid. *J. M. Research* **31** 63 1914

21 Halliburton W. D. The Possible Functions of Cerebrospinal Fluid. *Lancet* **2** 779 (Nov. 4) 1916

22 Sabin F. R. The Method of Growth of the Lymphatic System. *Harcov Lectures series II* New York 1915-1916

nate any other fluid in the body Weed² summarized the relationship of cerebrospinal fluid to the brain proper as follows

In one respect the cerebrospinal fluid does function as an accessory fluid to the central nervous system. The drainage of the fluid contained within the perivascular channels toward the subarachnoid space has been commented upon, this fluid really becomes added to the ventricular cerebrospinal fluid in the subarachnoid spaces. In that sense, then, these perivascular spaces represent accessory drainage channels, uninterrupted by cell membranes and capable of carrying toward the subarachnoid space the waste products of nerve-cell activity. Lacking a true lymphatic system, the nervous tissue apparently makes use of these perivascular channels as pathways for fluid elimination. The ultimate connection of these perivascular channels with potential spaces about each nerve-cell indicates the close relationship between the cerebrospinal fluid and the nervous system. And in addition to these rather obvious fluid spaces about the nerve-cells, there is evidence indicating that this fluid-system is intimately connected with the general tissue-channels through the ground-substance of the brain. The general direction of flow of this fluid under normal conditions seems to be toward the subarachnoid space. But under certain conditions this direction of flow may be reversed so that the cerebrospinal fluid passes from subarachnoid space to nerve cell (page 119)

CHANGES IN THE CHOROID PLEXUS

The choroid plexus is derived from a tufting of the ependymal lining of the ventricles. Each tuft is covered by a single layer of cuboidal epithelial cells which rest on a basement or limiting membrane (figs 1 and 2). The fibrous tissue of the stroma is minimal, and the basement membrane usually approximates the wall of a central blood vessel. Definite changes in the choroid plexus have been noted in cases of fatal injury to the head. The most striking alteration is seen in the connective tissue of the stroma in which varying degrees of edema occur. In some instances there is but little distention of the connective tissue, in others diffuse swelling of the cells has occurred (fig 3). In the most marked instances the villus is ballooned out with fluid so that the basement membrane is separated to the greatest extent from the underlying blood vessel (fig 4). The fluid causing this edema may be seen to collect in large spaces between the walls of the blood vessels and the basement membrane of the choroidal epithelium (fig 5). In some instances the accumulations of fluid are small and numerous, simulating bubbles, in others they may be large and cause a breaking down of the intervening septums. The blood vessels may be enlarged and distended, indicating hyperemic changes. The connective tissue cells may show swelling of the nucleus so that it appears vesicular and more round or oval than usual. These cells may take bizarre shapes and may be vacuolated. Pigmentation in the form of small granules is often present in the epithelium and stroma. The pigmented granules are usually contained in phagocytic cells. This pigmentation has been described by Flather²³ as

²³ Flather M. D. A Study of the Hemosiderin Content of the Choroid Plexus, *Am J Anat* 32 125 (Sept) 1923

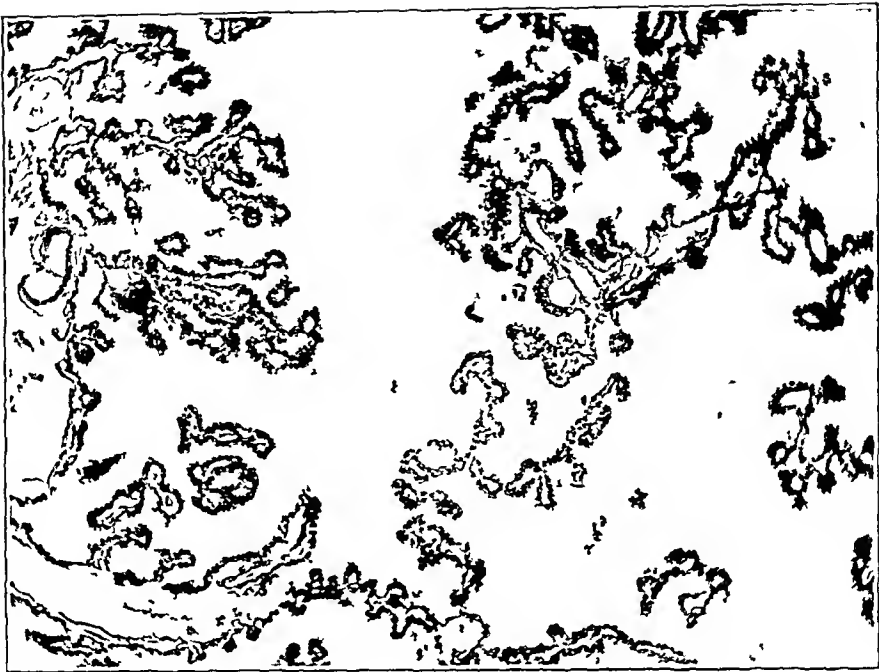


Fig 1—Normal choroid plexus. Various tufts of choroid plexus are seen. These are covered by a single layer of epithelium. The basement membrane on opposite sides of each villus is practically in coaptation, except where it is forced apart by the vessel. The stroma is inconspicuous, except near the pedicle of the gland. Hematoxylin and eosin stain, $\times 180$.



Fig 2—Normal choroid plexus. Tufts of normal choroid showing the proximity of the wall of the central artery to the basement membrane of the choroidal epithelium. A few small vacuoles can be seen in the epithelial cells. Hematoxylin and eosin stain, $\times 550$.



Fig 3—Moderate edema of the choroid plexus. The connective tissue of the stroma is moderately filled with fluid, forcing apart the choroidal epithelium. The spaces between the blood vessels and the choroidal epithelium are also widened. "Fibrin thrombi" are conspicuous. Those are not considered pathologic, as they are often seen in normal cases. Death occurred two hours after injury. Hematoxylin and eosin stain, $\times 190$.

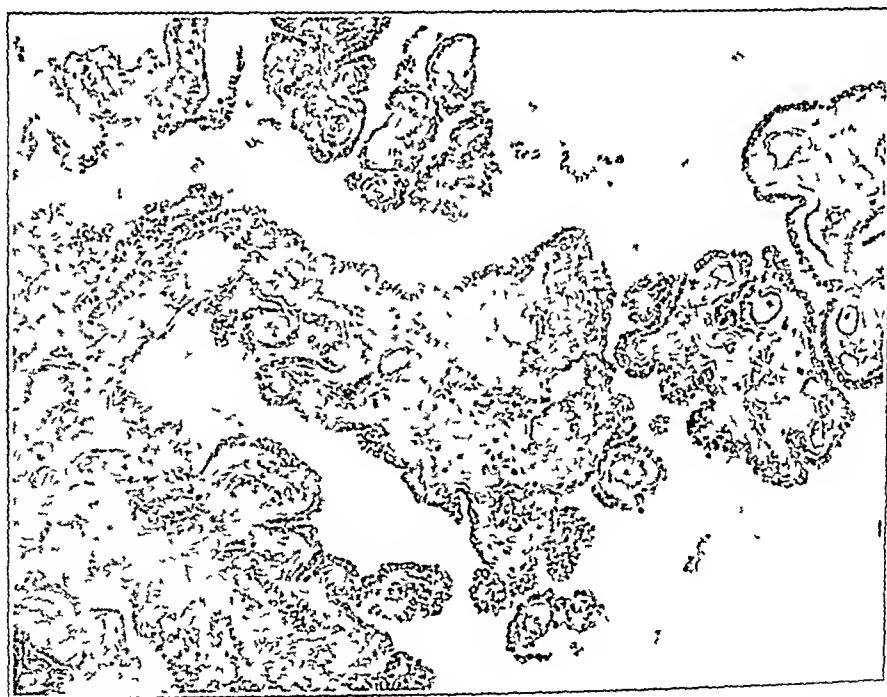


Fig 4—Marked edema of the choroid plexus. The stroma is expanded to the fullest extent by fluid. The choroidal epithelium is forced far apart, and the distance between the blood vessels and the basement membrane is greatly widened. Areas of pigment may be seen. This represents maximum edema of the choroid seen in this series. Death occurred four hours after injury. Hematoxylin and eosin stain, $\times 190$.

hemosiderin, but it appears to be noniron pigment, possibly hematoidin, as demonstrated by the specific reaction to the test with potassium ferriocyanide. Masses of "fibrin thrombi" are sometimes found in normal, as well as in pathologic, cases, which contain iron pigment as demonstrated by the same test. They usually increase in numbers as age advances.

The basement membrane is found to be intact when the accumulation of fluid within the connective tissue is small. When the edema is more extensive, free fluid is found in large spaces in the stroma and the basement membrane is often torn. In certain instances it is distorted, or even totally destroyed, so that the inferior aspect of the epithelial cells is extensively irregular and it appears as if fluid were being forced



Fig 5—Enlarged collections of fluid in the choroid plexus following injury. A marked increase in the fluid spaces between the blood vessels and the basement membrane of the choroidal epithelium is seen. There is a definite increase in the vacuolization of the cells. A vacuole in the process of rupturing is seen at the top. In several locations pigment granules, indicated by arrows, may be seen. Death occurred two days after injury. Hematoxylin and eosin stain, $\times 850$.

between them. The individual choroidal epithelial cells were often swollen and enlarged. In comparison to choroidal epithelial cells of normal height, i. e., 12 microns, cells varying from 14 to 20 microns in height are found, depending on the degree of edema. In certain instances cells measuring as high as 26 microns have been encountered. Often the free or ventricular margin of the cell is ragged, probably owing to its rupture by the passage through it of the contents of one large or many small vacuoles as they empty into the ventricle.

Vacuolization of the choroidal epithelium is normally seen in approximately from 12 to 20 per cent of the cells. The vacuoles may be multiple, in which case they are seldom large. Following trauma, vacuolization is greatly increased and may involve from 25 to 67 per cent of the cells. The vacuoles are often much larger than one sees in normal choroidal epithelium. Single vacuoles actually larger than a normal epithelial cell have frequently been observed (fig 6). The process of the formation of these vacuoles is not clear. Some have thought that they result from a coalescence of granules in the cells. From our study it would appear



Fig 6—Large vacuole of choroid plexus about to rupture into the ventricle. There are many fine vacuoles scattered throughout the epithelial cells. To the left of the large central vacuole, which points toward the free margin, one sees a collection of minute vacuoles apparently coalescing to form a large one. Marked edema of the stroma and a moderate irregularity of the basement membrane are seen. The choroidal epithelium is markedly distorted. Death occurred four hours after injury. Hematoxylin and eosin stain, $\times 1,800$.

that in certain instances fluid pushes up through the basement membrane of the cells, actually causing the formation of vacuoles within that structure. Some observers have described various inclusions of cells in the choroidal epithelium as being due to fat or to hyalin. In our preparations

fat stains (Nile blue and scharlach R) failed to demonstrate the presence of fat, and hyaline stains (van Gieson) still showed them as clear spaces in the cytoplasm. Increased granulation of the cells has been noted, but we have not seen condensation of the granules at the base of the cells and rarefaction at the apices, as has been described by other observers (Weed,¹ Pettit and Girard,⁶ Meek,¹¹ etc.)

CHANGES IN THE EPENDYMA

The ependymal lining is composed of a single layer of epithelial cells which are attached to the underlying substance of the brain by a very thin basement membrane (fig. 7). The cells vary in height

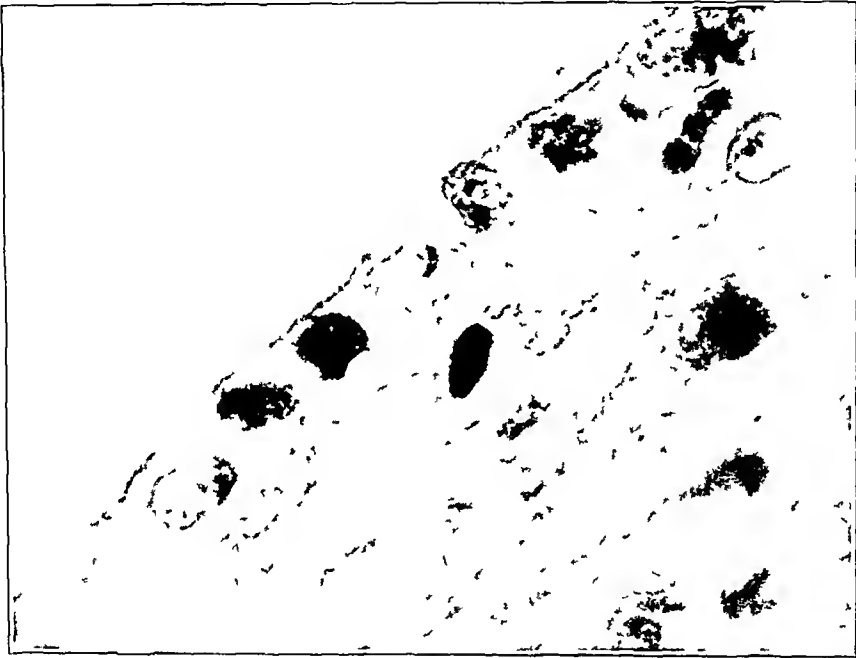


Fig. 7—Normal ependyma. The lining membrane is uniform, in places it appears ciliated. Several small vacuoles can be seen between or below the nuclei. The basement membrane of the cells is not clearly defined. The type of cell apparently is cuboidal. In certain instances the normal ependyma may be considerably more vacuolated than is shown here. Hematoxylin and eosin stain, $\times 1,800$.

in different parts of the ventricular system, but become more columnar as they approach the choroid plexus. Normally, the lowest type of cell measures about 5 microns, the cuboidal type from 6 to 9 microns, and the columnar type, near the pedicle of the choroid plexus, from 11 to 13 microns in height. There has been some evidence that fluid may pass normally through the ependymal lining from the brain into the ventricle or under certain conditions, such as internal hydrocephalus,

in the reverse direction Weed,²⁴ in discussing the elaboration of cerebrospinal fluid, stated that "a minimal production by the ependymal cells, negligible in its significance and total amount, may occur" Wislocki and Putnam,¹⁸ as well as Nañagas,¹⁹ have shown that in cases of experimentally produced hydrocephalus prussian blue was precipitated in minute granules both in the cytoplasm of the ependymal cells and in the perivascular and pericellular spaces of the substance of the brain beneath. They concluded that under certain circumstances both trypan blue and prussian blue found a definite pathway of escape from the

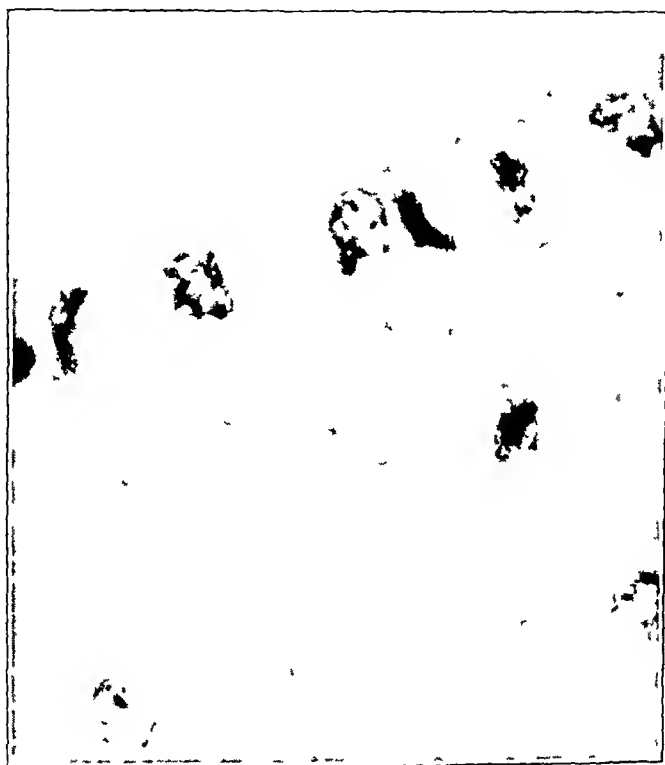


Fig 8—Moderate edema of the ependyma. Here moderate vacuolization of the ependymal cells is seen. The nuclei are distorted and the cells are heightened. In two places collections of fluid seem on the point of emptying into the ventricle. Considerable increase of the subependymal fluid spaces is also evident. Death occurred within thirty-six hours after injury. Hematoxylin and eosin stain, $\times 1,750$.

ventricles, through the ependyma, into the intercellular spaces and thence into the perivascular channels.

In our series certain changes in the ependymal lining and subependymal tissue have been found (fig 8). In the latter, varying degrees of edema occur. In certain instances the fluid spaces may be

²⁴ Weed, L. H. An Anatomical Consideration of the Cerebrospinal Fluid. *Anat Rec* 12:465 (May) 1917.

moderately enlarged, in others the stroma is ballooned out to such an extent that the trabeculae or septums dividing the individual channels are broken down. The basement membrane may be ruptured by fluid pressure and under certain circumstances almost completely destroyed (fig 9). Vacuolization of the cells is usually increased in varying degrees. The vacuoles or fluid spaces are much more numerous and larger than occur normally and may push the nuclei into eccentric positions. Not uncommonly the nuclei appear to be pushed forward toward the distal end of the cells in a palisade manner. They almost give the

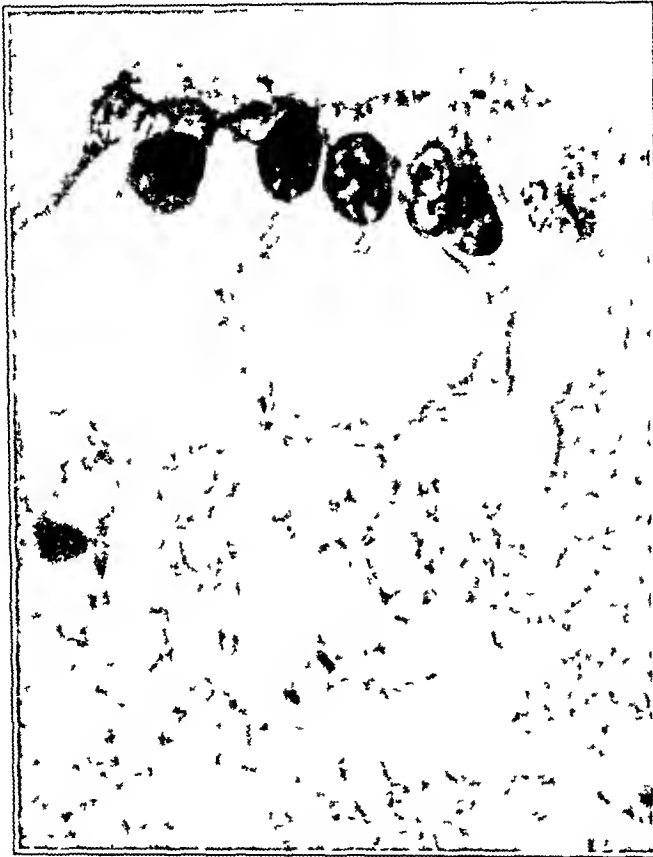


Fig 9—Marked distortion of the edematous ependyma. Great edema of the subependymal tissue is evident. The cells are tremendously heightened and filled with fluid. The subependymal fluid spaces are dilated and wide open. The nuclei apparently were forced forward by fluid. The lining membrane is irregular and in places is broken. This represents the maximum change found in the ependyma and the subependymal tissue in this series. Death occurred forty-eight hours after injury. Hematoxylin and eosin stain, $\times 1,750$.

appearance of having been floated up from their normal position. The height of the ependymal cells is also increased, depending largely on the amount of edema or vacuolization present. In cases of so-called "full-blown" edema of the ependymal lining, cells measuring from

30 10 to 32 25 microns have been observed. In cases of more moderate edema, cells of lessened height varying from normal to the aforementioned measurements have been seen.

Naturally, under the conditions described the outlines of the cells become irregular, often assuming most bizarre shapes. This is thought to be occasioned by the varying degrees of distention and vacuolization. In certain instances the free lining of the cells is fragmented, and if blood is present in the lateral ventricles, erythrocytes in varying degrees of degeneration may be found clinging to the free ependymal lining.

CHANGES IN THE SUBSTANCE OF THE BRAIN

Based largely on the hypothesis of a direct connection of the perivascular with the perineuronal and pericellular spaces—Vinchow-Robin spaces—one may attempt to explain certain histologic changes found in the substance of the brain following injuries to the head. The connection between these spaces has not yet been definitely proved. This system has been called on by some to explain the mechanism of concussion. Mott²⁵ (1919) hypothesized that a shock transmitted to the fluid occupying the ventricles and the subdural, perivascular and pericellular spaces would be passed directly to the neurons themselves. He explained concussion as a result of this transmitted effect on the nerve cells. Cassasa²⁶ (1924) explained the mechanism of concussion in much the same way. He found an overfilling of the perivascular spaces with cerebrospinal fluid. He also expressed the belief that the fine fibrils as described by Mott²⁷ (1910), connecting the outer surface of the blood vessels with the surrounding brain, are torn by stretching and that frequently the wall of the vessel is lacerated. He explained perivascular hemorrhages in this way. He expressed the opinion that the cerebrospinal fluid is forced down the perivascular spaces from the subarachnoid spaces in a direction opposite to its usual flow and thus explained the distention of these spaces. It will be recalled that Weed¹ stated that "under certain conditions this direction of flow may be reversed so that the cerebrospinal fluid passes from the subarachnoid spaces to the nerve cells." Cassasa²⁶ felt that the direct physical changes thus caused in the ganglion cells of the brain might well explain the phenomenon of concussion.

25 Mott, F. W. *War Neuroses and Shell Shock*, London, Oxford University Press, 1919, pp. 4 and 5.

26 Cassasa, C. B. Multiple Traumatic Cerebral Hemorrhages, *Proc. New York Path. Soc.* **24**: 101 (Jan-May) 1924.

27 Mott, F. W. The Pathology of the Cerebro-Spinal Fluid, *Lancet* **2**: 1 and 79, 1910.

There is probably a close analogy between the "water brain" produced experimentally by using intravenous hypotonic injections and the "wet brain" seen following severe injuries to the head. Naturally, the changes in the latter condition, while similar, would not be as marked as those which could be produced in the laboratory. Ferraro²⁸ (1930) recently studied the subject in rabbits. He found changes in the choroid, ependyma and tissue of the brain proper, which are practically analogous, though much more marked, than those seen after severe injuries to the head. He described increased vacuolization of the choroid plexus, and increased subependymal edema with disruption of the epithelial lining membrane. He also described increased edema of the interstitial

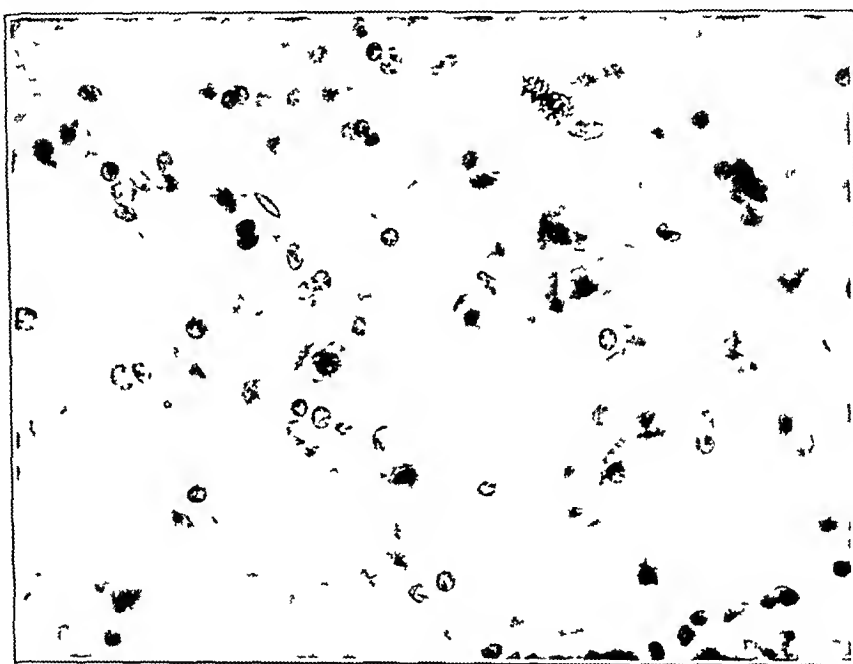


Fig 10—Normal substance of the brain, frozen section to eliminate artefacts. Several pyramidal cells are shown. No pericellular space is present, except as faintly indicated about one pyramidal cell at the upper right corner. At the lower right corner a vessel can be faintly seen, but the perivascular space is not evident. Hematoxylin and eosin stain, $\times 335$.

tissue of the brain in various localities, as well as dilatation of the perivascular and pericellular spaces and even vacuolization of the nerve cells proper. In addition he has shown acute swelling of the glial elements (oligodendroglia and microglia), as well as pronounced swelling of the lining endothelium of the intima of certain small blood vessels.

Frozen sections have been employed in order to eliminate as far as possible the error that may be caused by uneven contraction of tissue

²⁸ Ferraro, Armando. The Reaction of the Brain Tissue to Intravenous Injection of Hypotonic Solutions, *J Nerv & Ment Dis* 71:129, 1930.

when paraffin or celloidin is used. This practically eliminates the production of artefacts (fig 10). We have found an increase in the size of the perivascular and pericellular spaces in this series of fatal injuries to the head (fig 11).

The question of how the fluid reaches these spaces appears to be the crux of the whole matter in seeking to explain edema of the brain from any cause. If a potential communication between the perivascular and the pericellular spaces exists, as Weed¹ would have one believe, it is conceivable that cerebrospinal fluid may be forced down the perivascular spaces in a reverse from the normal direction and thus overfill the pericellular spaces. This communication, however, has not yet been

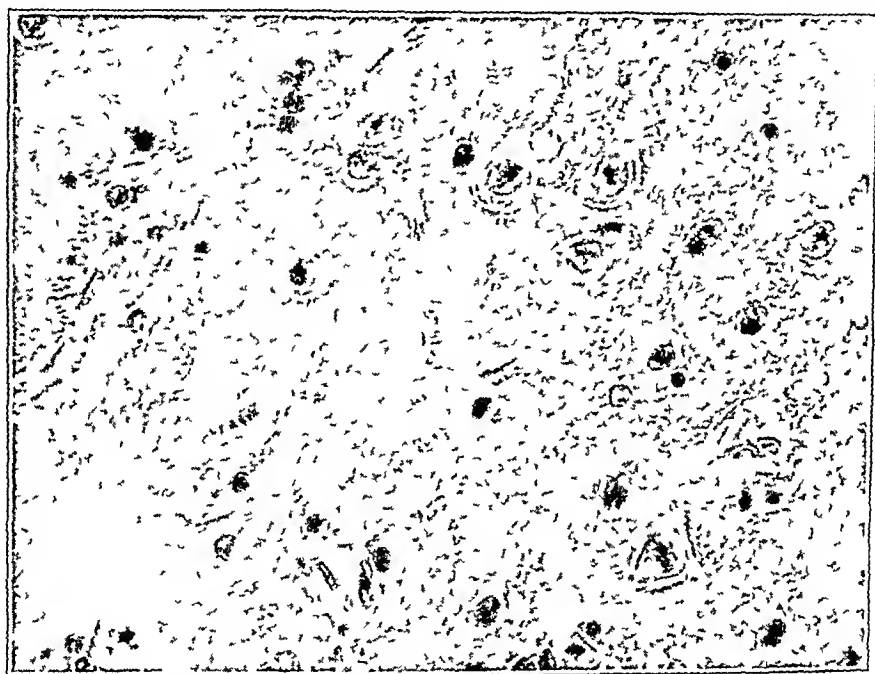


Fig 11—Edematous substance of the brain, frozen section to eliminate artefacts. Definite pericellular spaces are present about many cells. These spaces are enlarged and are believed to be filled with fluid following trauma. To the left and above, an enlargement of a perivascular space is clearly seen. Death occurred one hour after injury. Hematoxylin and eosin stain, $\times 335$.

absolutely demonstrated. On the other hand it would appear that edema of the brain may not be essentially different from edema occurring after injury in any other tissue of the body. May not fluid pass directly through the semipermeable membranes lining the smallest capillaries into these perivascular spaces, under both normal and pathologic conditions? In case of injury may not the amount of accumulating fluid be increased, thus giving rise to distention of both the perivascular and the pericellular spaces? If such a condition exists, and theoretically there is no reason why it cannot exist in the brain as in any other

tissue, no assumption of the reversal of the direction of the flow of fluid in the perivascular spaces would be necessary. One could assume that the fluid passes in increased amount directly through the semipermeable wall of the vessel, distending the perivascular and pericellular spaces, and continues to flow back toward the subarachnoid spaces where it is absorbed in the usual channels.

In papers to follow, the changes outlined will be taken up in greater detail.

PERIOSTEUM

A LIVING BONE SUTURE *

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Delayed union and nonunion in fractures of the long bones has for years been a fertile field for investigation and the source of much thought by surgeons specializing in conditions of the bones and joints. Many theories as to the cause of the aforementioned conditions have been advanced. Chief among them should be mentioned (1) insufficient immobilization by improper splinting, (2) infection, either primary due to compounding of the fracture, or secondary, due to lack of aseptic technic at open reduction, (3) previous or concurrent organic disease, such as syphilis, tuberculosis, etc., (4) general asthenia with low metabolic rate and diminution in the cellular and hemoglobin content of the blood, (5) the lowered calcium phosphorus content of the blood as determined by laboratory methods, (6) interposition of tissue, such as muscle, fascia, fat, etc., (7) the type of suture material selected for internal fixation, such as various forms of catgut, kangaroo tendon and all metal fixative agents. After studying the numerous textbooks on fractures and dislocations, one finds that this problem of delayed union is passed over in a more or less perfunctory manner, and little attempt is made to lay emphasis on minimizing the risk of delayed union and nonunion by the selection of proper material for internal splinting and on the necessity of studying the patient as an organic whole. One should mention here the research of Petersen of Johns Hopkins, in which he studied the calcium-phosphorus content of the blood and was able to predict nonunion in those animals which showed the percentage of these chemicals below a certain level. This may explain some of these cases, but the mechanical factors of improper fixation and disturbance of circulation in the fragmented ends is another problem.

Nonunion and delayed union follow operative intervention in a far higher percentage than in the nonoperative type. For many years without due thought and consideration, surgeons have been prone to lay the disaster at the door of the artificial suture as the inciting cause. The experimental work of Groves, published in the *British Journal of*

* Submitted for publication, June 5, 1930

* From the Hygienic Laboratory of the United States Public Health Service, Washington, D C

Surgery (1913-1914), which discusses the operative intervention in fractures, leads one to the definite conclusions that

1 Sepsis is not an infrequent result in the hands of the average surgeon

2 Nonunion and delayed union result in about 40 or 50 per cent of all fractures so treated. This is due to the interference of the circulation in the ends of the bone fragments, affecting chiefly the meager circulation of the periosteum, and thus preventing the formation of early callus

3 The use of absorbable sutures, absorbable pegs or absorbable bone plates frequently brings about delayed union, because these substances break, fracture or bend before sufficient callus has been thrown out to immobilize the fragments satisfactorily. Groves also stated

The periosteum is the product and not the mother of bone, all osteogenetic properties of the periosteum, whether in repair of fractures or in grafting, are due to the presence of the outer layer of the bone cells adherent to its deep surface. Living bone is the chief source and origin of callus which grows mainly from its outer, or periosteal surface, to a less extent from its deep or medullary surface and its cut ends

This quotation offers the suggestion that periosteal callus is important in the early stages of bone repair

An account of the researches of McEwen in his study of bone repair, and of Johnson in the *Journal of Bone and Joint Surgery*, July, 1927, in which both of these writers assert that the heaviest and strongest callus is thrown out by endosteal and medullary bone, gives one an excellent picture of permanent and firm union. The studies of these three men, Groves on the one side and McEwen and Johnson on the other, do not directly contradict each other for the one is dealing with early proliferation and repair of the bone, the others with late repair and permanent union. The fixation of fragments of bone by early periosteal proliferation will aid materially in increasing circulation, and hence will act as a stimulant to the permanent and strong endosteal callus. This conclusion would seem to obtain in those cases in which large drill holes are utilized and steel screws, kangaroo tendon or steel wire are used for fixation

In reviewing seventy-six cases of open reduction of the long bones at the Emergency Hospital in Washington, D. C. from October 1926, to October 1928, one is impressed with the high percentage of nonunion and delayed union. One must remember however that these patients were operated on by a variety of general surgeons and the percentage of delayed union and nonunion is probably higher than that of a well organized fracture clinic

Only nine of these open reductions were followed by sepsis, and therefore the lack of healing of the fractures cannot be laid to improper aseptic technic. A large number of the ununited cases of fracture of both bones of the forearm is outstanding. In all of these cases, since sepsis was negligible, the delay was due either to the use of foreign suture material or to ineffectual immobilization by improper splinting. The comparison is striking, presenting 82 per cent delayed union and nonunion in the cases in which suture was employed as contrasted with 13 per cent in which it was not used. The types of suture used consisted entirely of kangaroo tendon and silver wire, no plates being used. In the analysis of this group open operation on the humerus showed no single case of delay. In fractures of the tibia, those of the lower third were conspicuous, there being 42 per cent in which suture was employed and 20 per cent in which this procedure was not used. The femur showed a delay in 25 per cent of the cases in which suture was

TABLE 1—Data on Seventy-Six Cases of Open Reduction of the Long Bones

		Total	Union	Nonunion	Sepsis	Nonunion, per Cent	Total Nonunion per Cent
Radius and ulna	Sutured	11	2	9	0	82	43
	Unsutured	15	13	2	2	13	
Tibia	Sutured	17	9	8	4	42	41
	Unsutured	5	4	1	1	20	
Humerus	Sutured	4	3	1	0	25	16
	Unsutured	2	2	0	0	0	
Femur	Sutured	12	9	3	2	25	23
	Unsutured	1	1	0	0	0	
Clavicle	Sutured	8	8	0	0	0	0
	Unsutured	0	0	0	0	0	

done, zero in those in which it was not done. Not a single case of nonunion of the clavicles was observed.

Routine roentgen studies showed no early periosteal callus and little endosteal callus at the end of several weeks. The bones were atrophied and the fragmented ends eburnated. It is noted that the greatest percentage of nonunion occurred in bones of the forearm, although the tibia and the femur are fairly frequent offenders.

Wiring and suturing practically have been discarded because of such untoward results. The cause may partially be explained by the reasons

- 1 The medullary cavities of the ulna and the radius are small
- 2 The periosteum and cortex are thin
- 3 The insertion of any foreign suture interferes considerably with the blood supply in the ends of the fractured fragments
- 4 It would appear that good apposition of the fragments is absolutely necessary for satisfactory repair of a fracture and to minimize the chances of delayed union and of nonunion

5 Proper fixation is one of the fundamental principles, but this is often difficult to obtain, even with immobilization of the joint above and below the break, this is especially true of the bones that are surrounded by muscles of considerable strength and length

6 Adequate blood supply, both periosteal and medullary, should be preserved as carefully as possible. Groves, in discussing this, stated that the cortical bone adjacent to the periosteum is one of the prime factors of union, while Johnson, McEwen, Brown and Brown, and others expressed the belief that the repair is largely endosteal and medullary. In 1908, Axhausen stated that repair was both endosteal and periosteal.

7 In order to stimulate the blood supply, early mobilization of the fractured extremity is the proper procedure. This should be done as soon as is consistent with safety in maintaining the position of the fragments. It would seem, therefore, that an early callus sufficient to maintain fixation of the fragments would be ideal.

These are the cardinal principles of the treatment of fractures so that repair may take place in as short a time as possible and the dangers of nonunion may be minimized.

The necessity of internal fixation in a large number of operative cases is paramount. It would seem to follow from the foregoing facts that the sutures used heretofore, especially in the bones of the forearm and the tibia, have been unsatisfactory. Because of the importance of such a high percentage of delayed union in operative cases in which suture was used and the relative scarcity of delayed union in fractures well reduced by closed reduction or in open reduction without suture, it would also seem that an autogenous suture of some material would be the one of election. Silver wire, catgut, kangaroo tendon plates, bone plates, screws and bands all have a tendency to interfere with circulation to cause absorption, to invite infection, and in some instances to make for insufficient immobilization. Fascia lata has been used as an autogenous suture, but it lacks the quality of stimulating early callus formation.

The qualities of the ideal bone suture should be as follows:

- 1 It must be strong, i. e., strong enough to maintain position of the reduced fragments in the face of the muscle pull exerted on them.

- 2 It should be easy to obtain with the minimum loss of function to the part from which it is excised, and should subject the patient to as small an increase in operative risk as possible.

- 3 It should be nonirritating in order to minimize the chances of sepsis.

- 4 It should be autogenous since an autogenous tissue will not interfere with the blood supply but rather will tend to increase it in the parts to which it is grafted.

5 It should be osteogenic by virtue of its own properties in the bone fragments in order to aid early fixation by the formation of early normal callus

6 It should be of such a nature that it is easily inserted

In the physiologic laboratory the tensile strength of the following sutures was taken chromic catgut nos 2, 3 and 4, kangaroo tendon, medium and heavy, and living periosteum The tensile strength of silver wire, annealed iron or of twisted bronze wire was not tested,

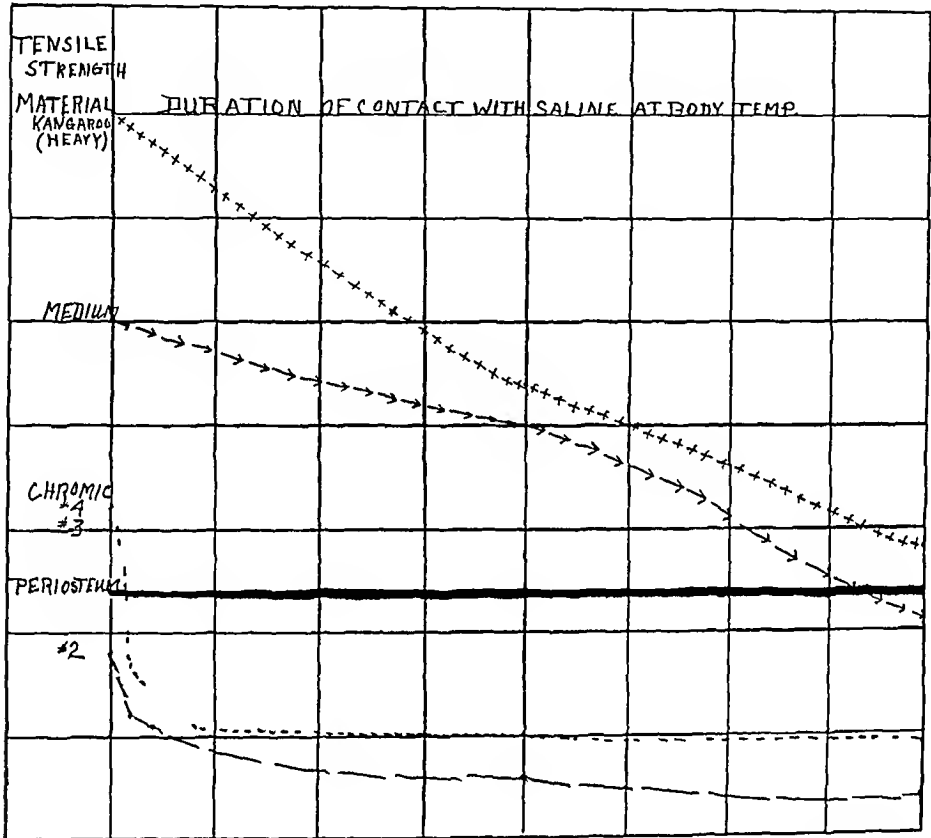


Fig 1—Relative tensile strength of absorbable materials placed in physiologic solution of sodium chloride at body temperature

because their tensile strength is a definitely known quantity. It is always constant in the brand of wire used and is much greater than any of the absorbable sutures. Figure 1 shows the relative tensile strength of these absorbable materials.

The materials used were as shown. All of these substances were placed in physiologic solution of sodium chloride at body temperature and were allowed to remain there over a period of several hours, in some cases as long as forty-eight hours. The breaking strength of these substances was determined at varying intervals, the simple

dynamometer scale being used and a load of weights sufficient to rupture the sutures applied. The diameters of the various materials were obtained by a micrometer screw and a cross-section area easily determined from these figures. The tensile strength of the substances, that is, the load sufficient to rupture a cross-sectional area was computed. The results were interesting, showing that all of the absorbable sutures had a definite diminution in their tensile strength, that diminution being directly proportional to the time of contact with the physiologic solution of sodium chloride. All the catgut and kangaroo tendons were strikingly hygroscopic and increased their diameter by as much as 100 per cent in many instances. The periosteum alone survived the long period of hydration and showed no change in its tensile strength or its diameter.



Fig 2 (rabbit 1) —A roentgenogram taken one week after fracture showing the unsplinted bone with extensive hemorrhage into the soft tissues, and no evidence of bony proliferation.

The foregoing experiment explains the conditions which are often seen following suturing of a fracture with an absorbable material. The catgut or kangaroo tendon, being hygroscopic, absorbs the tissue fluids about the site of fracture and is rapidly weakened by this physical property. Its tensile strength is much diminished, and the muscle pull is sufficient to break the fixative agent and allow a displacement of the bone fragments from forty-eight to seventy-two hours after operation. The occurrence of this phenomenon is well known to all surgeons. The periosteum when treated experimentally in this fashion shows no tendency to absorb fluids and since it is an autogenous tissue, should not do so in the human body, therefore its tensile strength should not be diminished in any way.

Histologically, the periosteum consists of three layers

1 The thick fibrous coat, which contains the blood supply and lends practically all of the strength to the tissue

2 The middle, elastic layer, containing chiefly the lymph supply This is a thin layer and is the tissue which permits the entrance of the external blood vessels to the cortex of the bone and allows a free bathing

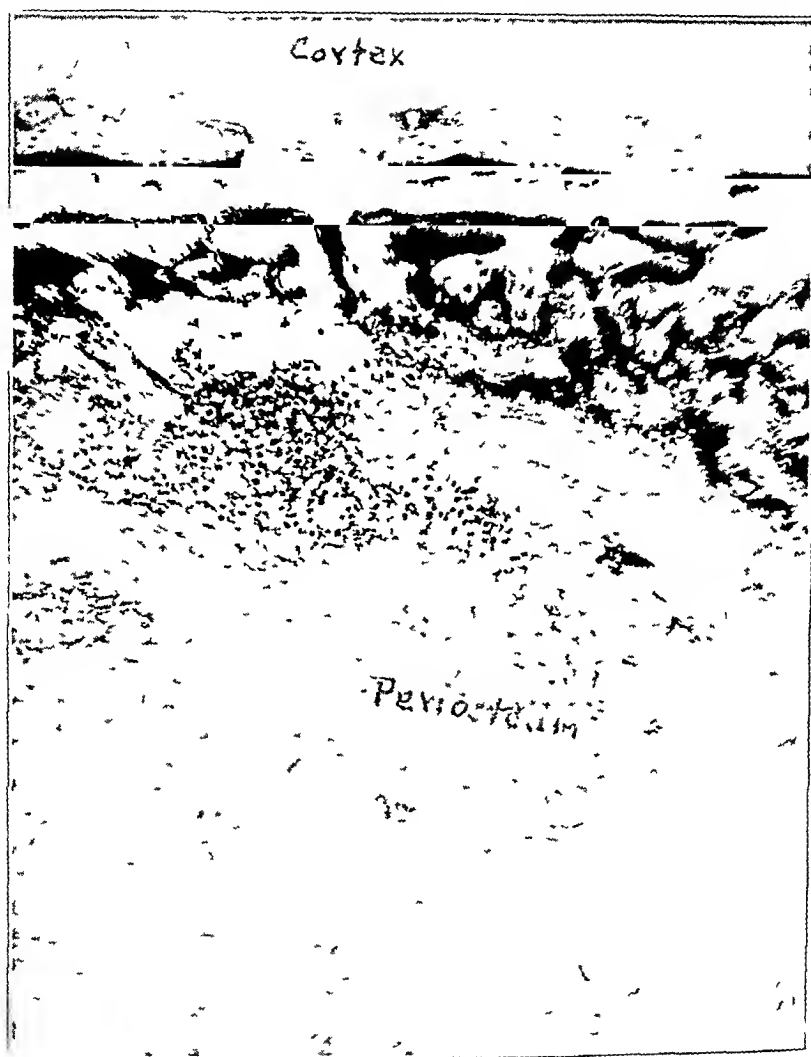


Fig 3 (rabbit 1) —Section stained by the silver method of Lillie, seven days after operation The black is calcium, there is early bony callus with an early calcification of the cartilage

of the osteogenic layer in the lymph, thereby furnishing nourishment to the osteogenic cells until they establish contact with the mother bone

3 The inner osteogenic layer which many histologists do not feel belongs strictly to the periosteum Whether this is true or not histologically, one can, with a little care, easily remove small scales from the

outer cortex of the bone with the fibrous periosteum. It is to these cells that we look for the osteogenic properties of this tissue.

The periosteum is an autogenous tissue and therefore nonirritating by virtue of this same property, it is nonhygroscopic, and as has been shown by the laboratory experiments previously mentioned there is no tendency to diminution of the tensile strength.

The periosteum is easily obtained from the anterior surface of the tibia, here it is thicker and stronger, and hence the valuable osteoblastic cells are readily obtained. This tissue can be removed with the minimum

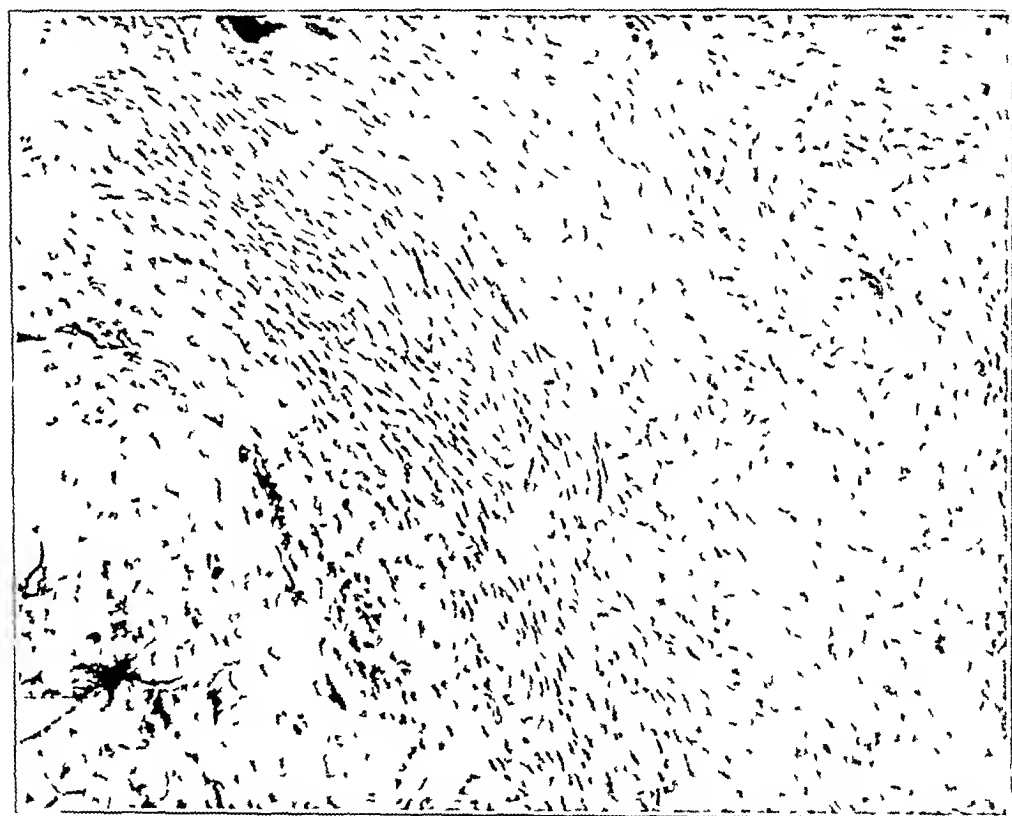


Fig. 4 (rabbit 1) —Section stained by the silver method, seven days after operation taken at the outer portion of the callus. Some calcification is seen in the cartilage, but none in the fibrous tissue.

amount of danger to the patient as the wounds in this region are superficial, easily dressed and heal readily with ordinary aseptic technique. There is no more risk of an aseptic wound under these circumstances than following fascia lata excision which is used as a living suture in a large number of plastic operations.

The periosteum is easily inserted. The technique for this type of suture is no more difficult than is the technique for any other material.

It has osteogenic properties. It is osteogenic if one is careful to remove small shavings of cortical bone with the fibrous periosteum. The

long-standing controversy as to whether periosteum is osteogenic is still apparently unsettled. Many valuable researches have been made on this subject, and many men of note have expressed diversified views. Such men as Ollier, Frankenheim, Lubenhoffer, Carrel, Axhausen, and Haas have championed the cause of periosteal proliferation in free transplant. Carrel stated that periosteum can be grown in the mediums



Fig 5 (rabbit 1) —Section stained by the silver method, seven days after operation, higher power. The cortical bone is densely stained. Many bony lamellae are seen between which are innumerable blood spaces. The lamellae are young because their margins are irregular.

of the laboratory, and the fairly recent work of Canti, who has recorded his work by means of the cinema, leaves no doubt that the osteoblasts of the inner layer are not only monoblastic cells, but multiply rapidly in the proper surroundings. Lubenhoffer goes so far as to say that in free bone transplants the bone dies, but the periosteum lives. Haas

modified his earlier statement, and said that periosteum proliferates best when opposed to cortical bone. Those who would controvert these statements are somewhat in the minority, chief among them is Barth, who stated that all bone degenerates when freely transplanted. Brown and Brown, in a large series of experiments, arrived at the conclusion that it did not live when freely transplanted, and that it was not necessary for the life of the bone. McEwen stated that all regeneration of bone is endogenic, while Johnson is inclined to agree with the experiments of Brown and Brown that the periosteum is not essential to the life or health of bone, because the periosteal blood supply penetrates



Fig 6 (rabbit 2) —A roentgenogram taken twenty-one days after operation showing the unsplinted bone, with a bone wax medullary plug. There is marked callus, mostly periosteal.

but a small portion of the cortex. The largest blood supply comes by way of the nutrient and metaphyseal arteries.

In the present brief for the periosteal suture, it matters not whether or not periosteum regenerates when freely transplanted. One conclusion of all men who have done research on the subject of periosteum is that periosteum grows best when in contact with bone, that it regenerates early in fracture repair thereby aiding blood supply and fixation. It is this early periosteal callus that is the conveyor of

increased blood supply to the fractured area, thus supplying increased nourishment for the formation of the strong endosteal callus which appears later. The essentials for its maximum value in its use as a suture are strength and the maintenance of strong proper fixation of the fractured bone to allow a good contact as early as possible and thus to enhance its osteogenic function in those cases in which nonunion is most probable and most common. It was from these facts and with the thought that it might be a desirable suture for certain types of fracture that the following experimental work was undertaken.

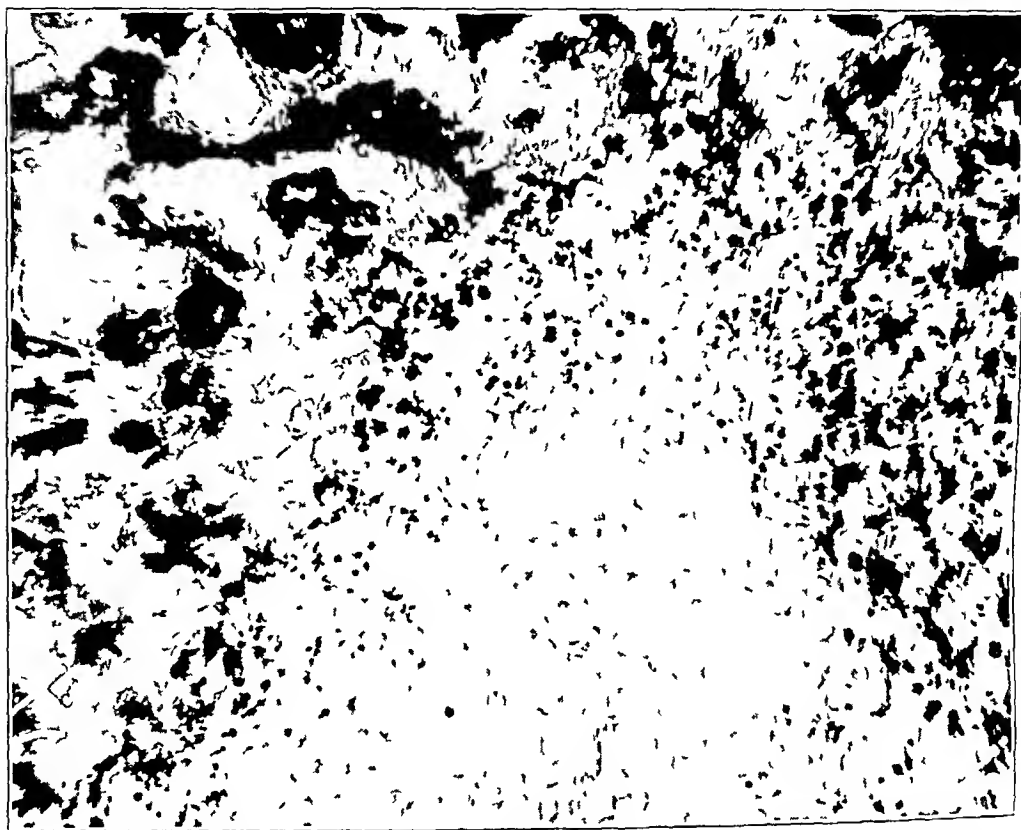


Fig 7 (rabbit 2) —Section stained by the silver method, twenty-one days after operation, higher power magnification. There is cancellous bone, periosteal in character, and early calcification of the cartilage.

This study was made not so much to determine whether or not periosteum lived in free transplant, or whether or not it was the main factor in the healing of fractures, but rather to determine just what its reactions were under the abnormal conditions of fracture in simple cases and in those fractures in which some substance was interposed between the ends of the fragments, as well as the effect of proper and improper splinting. This study was also made to determine what occurred when a broad section of periosteum was transplanted across an area without direct bone apposition except at the ends of the graft.

MATERIAL AND METHOD OF EXPERIMENTAL WORK

In all of these experiments rabbits were used, because they were found to be less susceptible to ordinary infections due to breaks in technique, and because the period of repair of rabbit bone is short. In all cases the tibia was the bone of election. The method used was to fracture the tibia manually before exposing the bone. This allowed a sequence of events to take place such as would normally be expected following a simple fracture, namely, comminuted and other bizarre types of fracture, hemorrhage from the fragment ends and the possibility of damage and injury to the soft tissues surrounding the bone. The periosteum was utilized in different cases, as will be shown in the protocols, in order to determine just what its reaction presented. In some instances the medullary

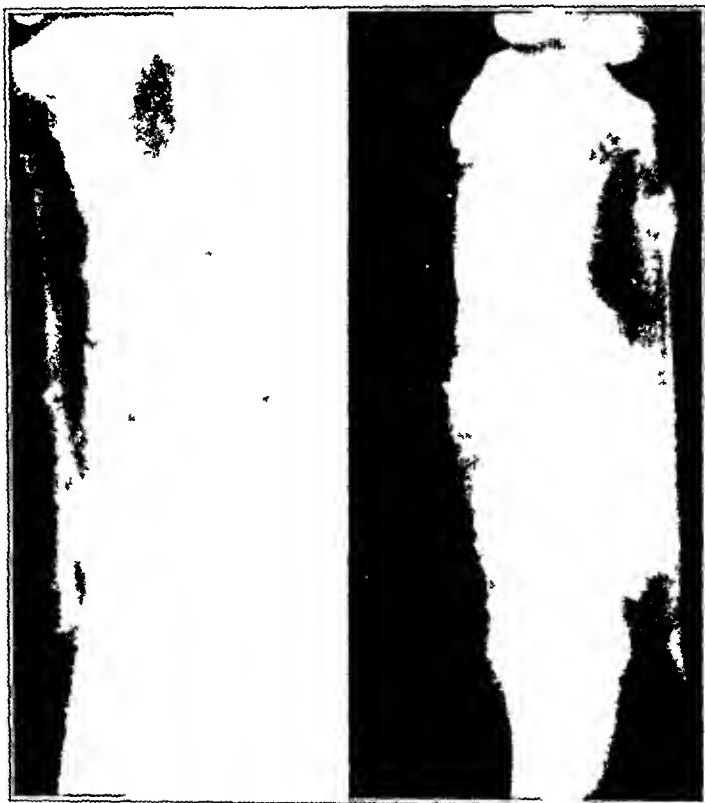


Fig 8 (rabbit 3) —A roentgenogram taken twenty-six days after operation showing the splinted bone, no bone wax was used. There is heavy periosteal and some early endosteal proliferation.

cavity was plugged with bone wax and the periosteal flap carried across the point of fracture, care always being taken to oppose the osseous surface of the periosteum at its point of contact with the cortex of the tibia. Skin closure was made in the usual way with plain 00 catgut. In some cases the leg was splinted effectually immobilized in coaptation splints or heavy adhesive plaster casts; in others it was bandaged loosely with gauze. The animals were allowed to move about freely. In no case was there any evidence of sepsis at autopsy. These rabbits were all healthy and had not been used for any other experimental purposes. Roentgenograms were taken of all the rabbits on which autopsy was performed.

with the exception of rabbit 1, which was killed at one week and rabbit 4 which was killed at twelve days after operation, the others were allowed to live for three and four weeks. Longitudinal and transverse sections were made and stained by three methods: the silver impregnation method of Lillie, the hematoxylin and eosin stain, and the van Gieson.

RABBIT PROTOCOLS

RABBIT 1—The tibia and fibula were fractured manually at the junction of the middle and upper third. The leg was not splinted, and the rabbit was killed at one week without operation.



Fig 9 (rabbit 3) —Section stained by the silver method. The cortical bone shows a very late callus, both the periosteal, the lamellae of which are densely calcified, and the endosteal, which is partly calcified. The periosteal callus is very vascular.

The roentgenogram showed an early callus formation consisting largely of hemorrhage, but with no definite bony proliferation. The fragments were in poor contact, and there was considerable angulation.

A microscopic section, stained with hematoxylin and eosin, showed a definite, early periosteal callus, with the osteoid tissue close to the bone and large masses of cartilaginous tissue which were slowly being invaded by the bone lamellae. Around the lamellae were large numbers of osteoblasts. There was no evidence whatsoever of any endosteum at this stage. The silver method of staining showed calcium salts deposited about the ends of the bones, entirely periosteal. The circulation of the proliferating periosteum was most abundant.

RABBIT 2—The tibia and fibula were fractured at the junction of the middle and upper third. After a subperiosteal resection, which was done as completely as possible, the ends of the bone were plugged with bone wax and the usual closure made, the periosteum being allowed to fall back into as nearly a normal position as possible. The leg was not splinted in any way.

A roentgenogram taken twenty-one days after operation revealed an overriding of the fragments with no end to end contact. There was, however, a fairly considerable bony callus extending from the end of one fragment to the side of the other and also filling up the space between the dislodged fragments. It was impossible to differentiate between endosteal and periosteal callus.



Fig 10 (rabbit 4) —A roentgenogram of the unsplinted bone taken twelve days after operation. No bone wax was used. Early periosteal, but no endosteal, callus is seen.

A microscopic section, stained by the silver impregnation method, showed a definite and thick section of osteoid tissue growing from the cortical bone. The periosteal callus under this method of staining revealed a large content of calcium salts and was extremely vascular, being filled with large blood spaces. At the outer side of this was a thick fibrous layer.

The outer coat of the periosteum in the other section taken transversely showed essentially the same picture, except that in one field it showed an early type of osteoid tissue which had not yet become calcified.

Under high power magnification, this same field in the early tissue, before calcium salts had thoroughly impregnated it, showed a definite matrix lined with calcium containing osteoblasts and all through the matrix itself were large numbers of black-stained cells

The same sections stained by hematoxylin and eosin showed the same picture, the calcium taking the deep hematoxylin stain and being lined with a large number of osteoblasts

In none of the sections of this rabbit was I able to pick out the formation of endosteal callus

RABBIT 3—This rabbit was treated in the same manner as rabbit 2 except that no bone was interposed. The periosteum was resected at its inferior



Fig 11 (rabbit 4) —Section showing early periosteal callus adjacent to the cortical bone with large blood spaces. While the calcification is heavy, the lamellae are immaturely developed

and superior attachments, the ends reversed and inserted in drill holes in either fragment. The leg was firmly splinted.

A roentgenogram, taken at autopsy twenty-six days after operation, showed the bone to have thrown out a large amount of callus. It was in good line in the lateral view, but in the anteroposterior view it had some medial angulation. There was a definite bridge of periosteal callus in both the medial and lateral sides of the tibia with a filling in of the spaces between this callus and the main cortex by firm bone.

The bones were firmly united clinically, and the rabbit was able to move about normally.

Microscopic sections stained by the hematoxylin and eosin method showed a striking proliferation of the periosteal tissue which was in all regions in close contact with cortical bone, very vascular, and at some points had begun to take on the characteristic appearance of normal cortical osseous tissue. The vascularity throughout was considerable. In this section, taken from a fractured tibia which had been completely immobilized, the bone seemed to be much more mature and there were fewer osteoblasts, the bone having more nearly reached maturity. Endosteal callus had appeared.

The section stained by the silver method showed a large amount of cancellous bone, thoroughly calcified and very vascular.

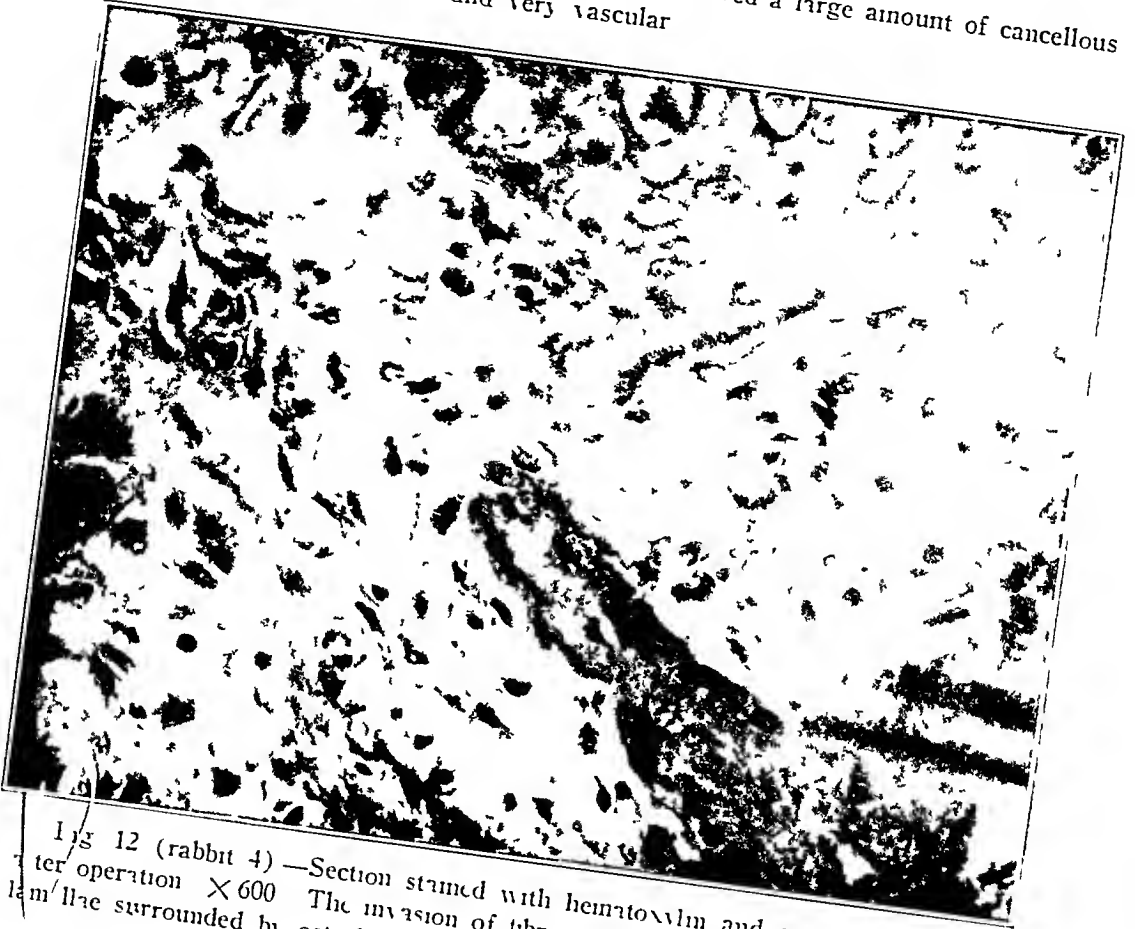


Fig. 12 (rabbit 4)—Section stained with hematoxylin and eosin twelve days after operation $\times 600$. The invasion of fibrous tissue and fibrocartilage by bony lamellae surrounded by osteoblasts is shown.

Rabbit 4—This animal was treated exactly as the others and an effort was made to force muscular tissue between the periosteum and the shaft of the bone. The leg was not splinted. A roentgenogram taken twelve days after operation showed an early beginning callus, but no bony union. Clinically there was no union.

Microscopic sections showed a large amount of osteoid tissue. There was good contact with the shaft of the bone itself; there was no medullary proliferation. There was some cartilaginous formation which was adherent to the osteoid tissue. In one section there was dense osteoid tissue and a large cartilaginous mass medial to which was some fibrous tissue, a blood clot, and cortical bone. The medullary cavity was free from any clot or debris.

RABBIT 5—A long incision was made over the medial portion of the tibia, extending above the knee joint. A long periosteal flap was then turned upward outside the capsule of the knee joint and fastened in a drill hole just above the medial condyle of the femur. There was no bony contact of the periosteum, except at its attached ends. The leg was thoroughly splinted after the usual closure had been made. Autopsy was done twenty-eight days after operation.

A roentgenogram taken directly after autopsy showed a definite periosteal bridge extending from the upper third of the tibia, around the capsule of the joint to the lower third of the shaft of the femur.

Transverse sections made through the condyles of the femur showed the compact bone of the condyle and the cancellous structures within, the fibrous



Fig 13 (rabbit 5) —A roentgenogram taken twenty-eight days after operation showing the splinted bone. Periosteal proliferation is seen along the line of the graft, outside of the medial capsule of the knee joint.

tissue of the capsule interposed between this condyle and a definite periosteal graft lying medial to this region.

RABBIT 6—The tibia was fractured after open operation, and the medulla was plugged with bone wax. The periosteum was left intact except for the long incision through which the subperiosteal resection was done. This leg was not splinted. Autopsy was done twenty-eight days after operation.

A roentgenogram showed poor position and periosteal proliferation.

Transverse sections taken through the area of fracture showed no evidence of endosteal callus, but a marked periosteal reaction, rather late because of much calcification.

RABBIT 7—This animal was treated exactly the same as rabbit 5, except that no immobilizing splint was applied

A roentgenogram showed no calcification in the region of the transplant

The microscopic sections showed no evidence of any periosteal graft

Conclusions—1 A periosteal graft, including small fragments of cortical bone, lives and proliferates when opposed to autogenous bone in situ

2 Periosteum is an early proliferative agent in the healing of fractures

3 Splinting affects the formation of periosteal callus materially, since periosteum is much more dense and tends to proliferate more actively in those cases which are carefully splinted and immobilized

4 Endosteal callus appears relatively late in the healing of fractures

5 Endosteal proliferation advances more rapidly and forms a firmer union when fixation is strong and when stimulated by an abundant, early periosteal callus

TABLE 2—Data on Calcification in Seven Rabbits

Rabbits	Time, Days	Type of Callus
I Not splinted	7	Early periosteal, but no endosteal callus
II Not splinted, medullary plug	21	Early periosteal reaction, calcification of cartilage, no endosteal callus
III Splinted, no bone wax	26	Heavy periosteal, and some early endosteal callus
IV Not splinted	12	Very early periosteal, but no endosteal callus
V Splinted	28	Periosteal proliferation
VI Not splinted, medullary plug	28	Late periosteal callus well calcified, no endosteal callus
VII Not splinted	28	No periosteal graft

TRACTION IN HUMAN FINGERS

I have had an opportunity to attempt the periosteal suture in several cases of fracture in human beings. Because of the experimental nature of the work care had to be taken in the selection of cases and an attempt was made to determine whether or not the periosteum had the properties desirable for an internal suture for fractures of certain bones. Several cases of fracture of the olecranon were selected in an effort to determine the following points: (1) whether it would hold the fragments in position, (2) whether it would proliferate as a suture and (3) whether it would aid in lessening the period of fixation normal for the healing of that particular fracture.

The periosteal suture was utilized in one case of ununited fracture of the humerus to hold the fragments in apposition after a step-cut operation was attempted. It was also used in one case of delayed union in the tibia, a broad flap of the periosteum being utilized. It has been used in one case of delayed union in fracture of the ulna. In several cases of fracture of the olecranon attempts were made to use the periosteal suture.

The operative technic is that of the insertion of any suture material. The fracture itself is first thoroughly exposed, the periosteum from the fragmented ends is carefully elevated from the shaft, and the direction in which the suture is to be applied is then decided on. Drill holes are carried through the shaft in the desired direction. A long incision is then made over the flat surface of the tibia, care being taken to incise only through the skin and subcutaneous fat. One should be extremely careful to preserve intact the outer coat of the periosteum, as it is this layer which lends its strength to the suture. With a sharp knife an incision is made through all layers of the periosteum down to and including the superficial layer of cortical bone. The strip should be from three-eighths inch to one-half inch in width, and as long as is necessary for the suturing of the bone fragments under operation. With a sharp elevator the same width as the

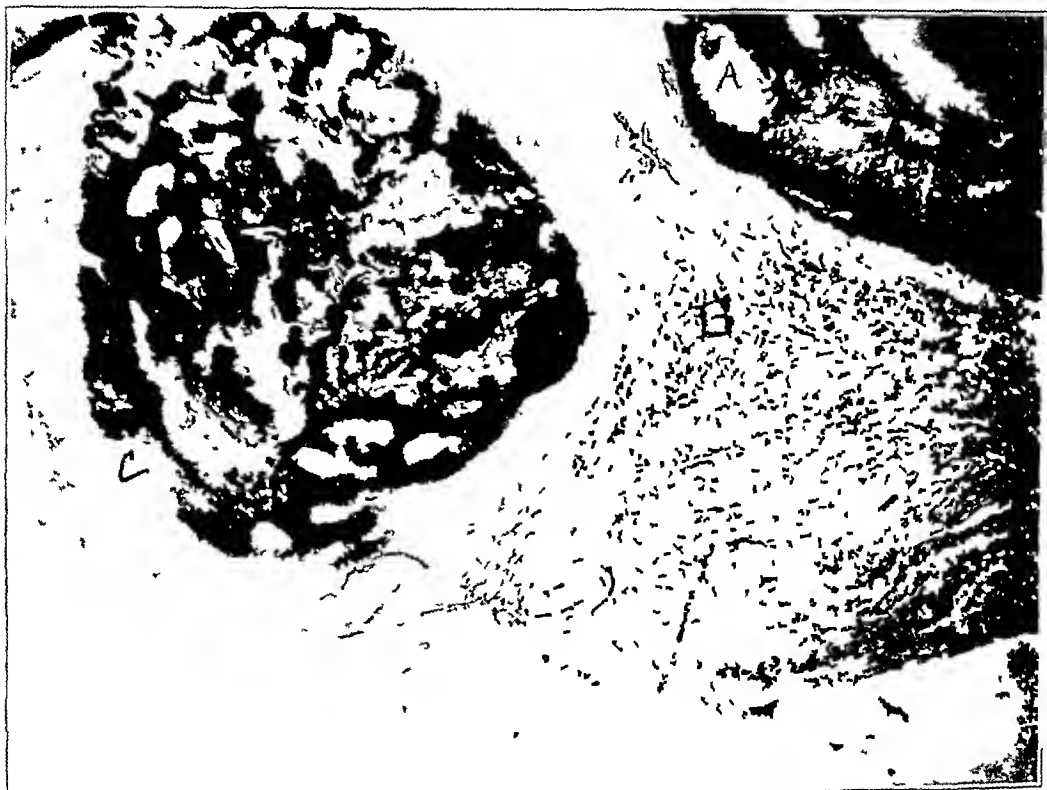


Fig 14 (rabbit 5) —Section stained by the silver method twenty-eight days after operation. *A* shows the condyle of the femur, *B*, the capsule of the joint and *C*, the periosteal graft which has proliferated extensively.

strip to be removed, the periosteum is carefully elevated from the bone with a rotating motion of the wrist and with firm pressure to insure removal of the small fragments of the outer layer of the cortex, for it is in this tissue that the proliferative qualities exist. The osteogenic-periosteal suture is then placed in warm salt solution for preservation, and the site of the fracture prepared for its reception. Small silver probes with specially devised eyes are utilized as the carriers and the suture carefully drawn through the previously made drill holes. The method of the insertion of the suture does not matter as long as it counteracts the natural tendency for displacement of the fragments. The figure-of-eight suture is an adequate method for fixation. The suture can be readily tied if the slight amount of natural elasticity which exists in this tissue is taken up, this is

easily determined by short experience. After the suture is in place and has been tied, care should be taken to flatten out and oppose the osteogenic surface of the periosteum to the cortex of the fractured bone. If there is any doubt concerning the fixation of the knot, one suture of chromic catgut no 2 may be passed through it and tied firmly, thereby preventing slipping. Following this, the periosteum which had previously been stripped from the bone is sutured over the transplanted graft. Closure is made in the usual accepted manner and the proper splint for the fracture under operation should be applied.

REPORT OF CASES

CASE 1—J G, a young colored man, had an untreated fracture of the olecranon which had occurred three months before. There was some separation



Fig 15 (rabbit 6)—A roentgenogram of the unsplinted bone taken twenty-eight days after operation. The bone wax medullary plug was used. In the anteroposterior view there is some periosteal, but no endosteal, proliferation.

of the fragments and no bony union. He was unable fully to flex and extend the arm.

At operation the olecranon was exposed in the usual manner, and fibrous union was found to have taken place. The fibrous tissue from between the fragments was carefully removed, but no curetting of the medullary cavity was done, nor was there any resection of the eburnated ends. A periosteal graft was removed from the tibia and inserted in a side to side figure-of-eight. Union was secured in the length of time normal to a fresh fracture. Ten weeks after operation the patient had the full use of his arm with no diminution of power.

Roentgenograms taken weekly during his convalescence showed a definite and steady increase in the proliferation of the graft. No medullary callus could be made out.

CASE 2—G, a young white woman, suffered a fracture of the olecranon in an automobile accident. There was some separation of the fragments, and operation was deemed advisable.

At operation the usual exposure was made with a periosteal suture passed through the posterior cortex of bone through the medullary canal, and tied posteriorly. Splinting consisted of fixation in a posterior metal elbow splint with the arm in about 45 degrees of flexion. Convalescence was uneventful, and at



Fig 16 (rabbit 6)—Section stained by the silver method twenty-eight days after operation. The cortical bone is seen with an extensive, well developed periosteal callus, no endosteal callus is present.

four weeks union was complete with definite evidence of periosteal proliferation. Active physiotherapy has been started and the patient is well on the road to recovery of complete function.

CASE 3—M W, a young colored girl, fell off the curbing, fractured her olecranon and displaced the shaft of the ulna anteriorly.

Operation was done, and a periosteal suture inserted because of comminution of the base of the olecranon process. It was thought wise to pass the suture

from side to side through the fragments of bone. This did not afford the proper fixation for the anterior displacement of the shaft, and it would have been better in this case to have laid the suture in the figure-of-eight in order to fix both displacements.

A roentgenogram made four days after the operation showed the shaft to be displaced slightly forward. The patient was taken to the fluoroscopic room, and the shaft forced backward to its normal position.

The bone fragments were in good position with fixation fairly firm after three weeks.

CASE 4—W. S., a colored man, fractured the olecranon and suffered slight skin abrasions in an automobile accident. Following his injury, a strepto-



Fig. 17 (rabbit 7)—A roentgenogram of the unsplinted bone twenty-eight days after operation showing no evidence of periosteal graft transplanted around the knee joint.

coccic cellulitis of the arm developed and was treated. In spite of the wide separation of the fragments, it was deemed inadvisable to operate in the face of this infection. Four weeks after the accident, when all clinical evidence of infection had subsided, open operation was attempted.

The usual method of approach was used, and a periosteal suture inserted. The olecranon was found to be rotated 90 degrees, but was easily brought into apposition and was firmly fixed with the graft. The incision over the tibia healed promptly per primum, but the incision over the elbow broke down in a few days and discharged the entire olecranon process. The infection evidently

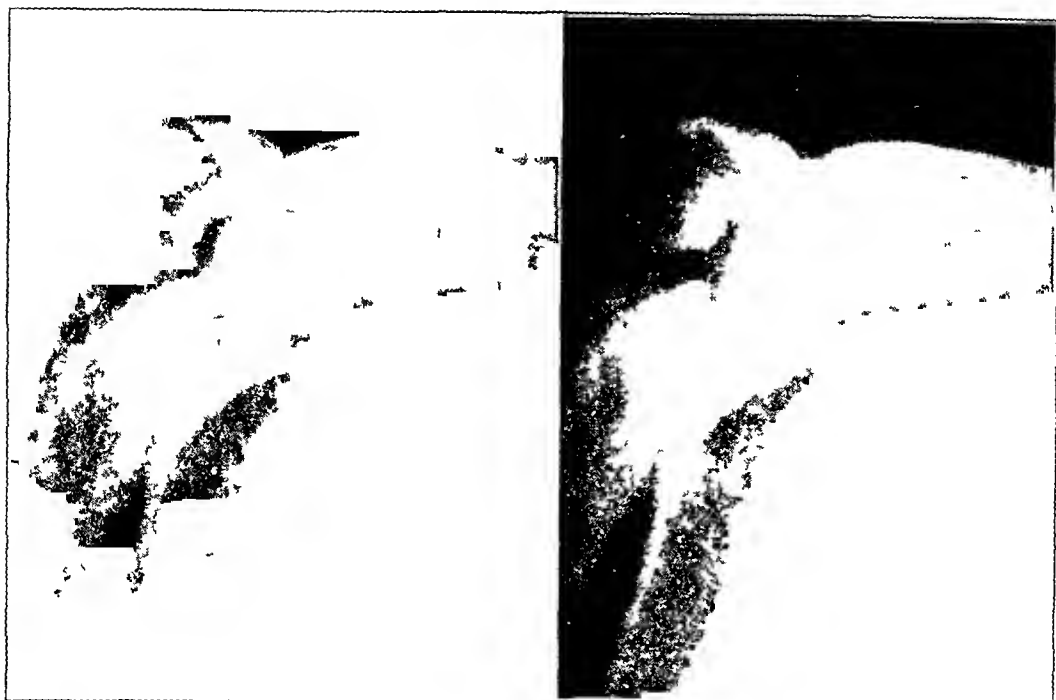


Fig 18 (case 3) —Roentgenogram taken before operation showing separation of the fragments and comminution of the upper end of the lower fragments



Fig 19 (case 3) —Roentgenogram taken ten days after operation showing the suture in place, with good apposition and firm fixation

had destroyed the graft, and the olecranon process, which was obviously necrotic bone at the time of operation, was promptly thrown off as a foreign body. After the evulsion of this fragment the wound healed, and at this date no further procedure has been instituted.

CASE 5—A M., a colored woman, who one year before operation fractured her tibia at the junction of the middle and upper third, had never had complete bony union, although the leg was strong enough to allow weight-bearing, but a small amount of motion could be made out at the site of the fracture. The Wassermann reaction was negative and the calcium and phosphorus in the blood showed no abnormal changes.



Fig. 20 (case 5)—Roentgenogram taken at the time of fracture one year before operation.

The site of the fracture and several inches more of the tibia was exposed. The periosteal strip from the fractured edges of the bone and a flap as broad as the anterior surface of the tibia itself were turned up over the fracture site and sutured beneath the periosteum of the upper fragment. The attachment at one end of the flap was left intact. A small slit was made in this flap, and another was brought down over the upper fragment and sutured into the periosteum of the lower. No attempt was made to invade the medullary cavity.

A roentgenogram showed some periosteal proliferation with an increase in the medullary callus after six or seven weeks.

This patient is now able to bear her weight freely, without pain and without sense of instability.

CASE 6—A K, a white woman, one year before operation suffered a compound fracture of the humerus. A serious infection ensued which cleared up with surgical treatment, but there was the characteristic picture of nonunion with a false elbow joint.

The roentgenogram showed the characteristic eburnated bone and a striking atrophy throughout the shaft. There was no evidence of any attempt at callus formation.

The step-cut operation was used. The atrophy of the bone was so great that the drill in passing through fractured a part of the cortex, breaking the step-cut.

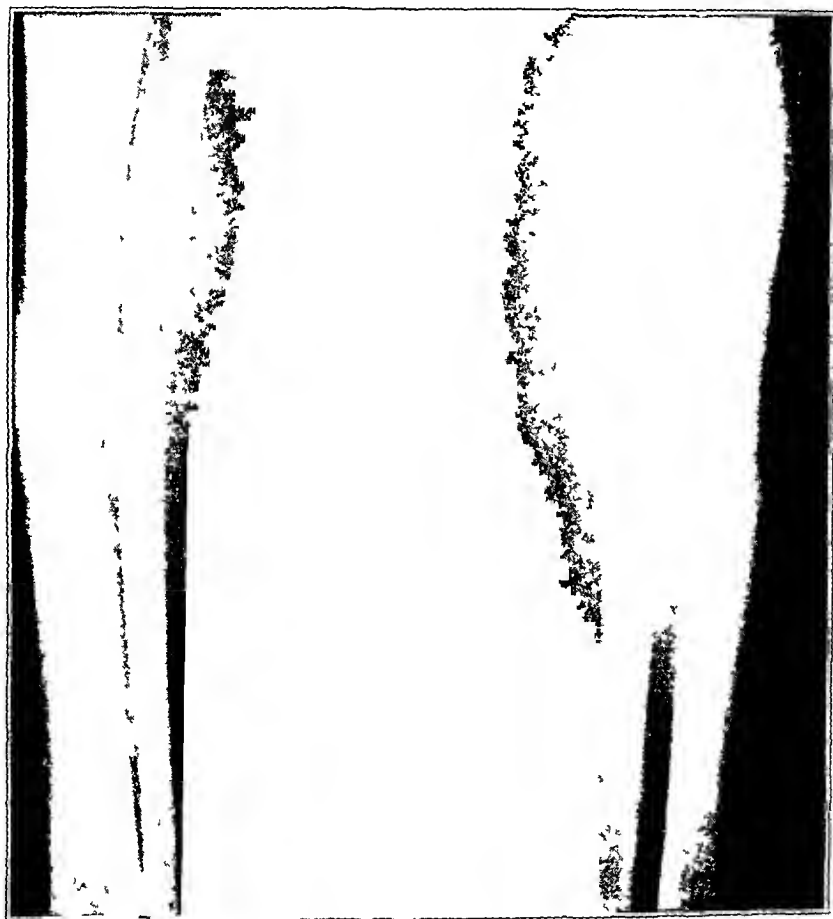


Fig. 21 (case 5)—Roentgenogram taken before operation showing fibrous union with good general alignment.

at its base. A periosteal suture was passed through both sides of the cortex above and below the cuts. Because the elbow could not be flexed, the patient was put up in a Thomas arm splint with no traction and with the splint at 90 degrees to the body.

Proliferation of the periosteal graft in this case was striking and early. Following this, the medullary callus proceeded to form a permanent callus. Six weeks after the operation, union was complete. Since that time the function of the elbow has been materially improved by physiotherapy, and the atrophy of the cortex is much diminished.

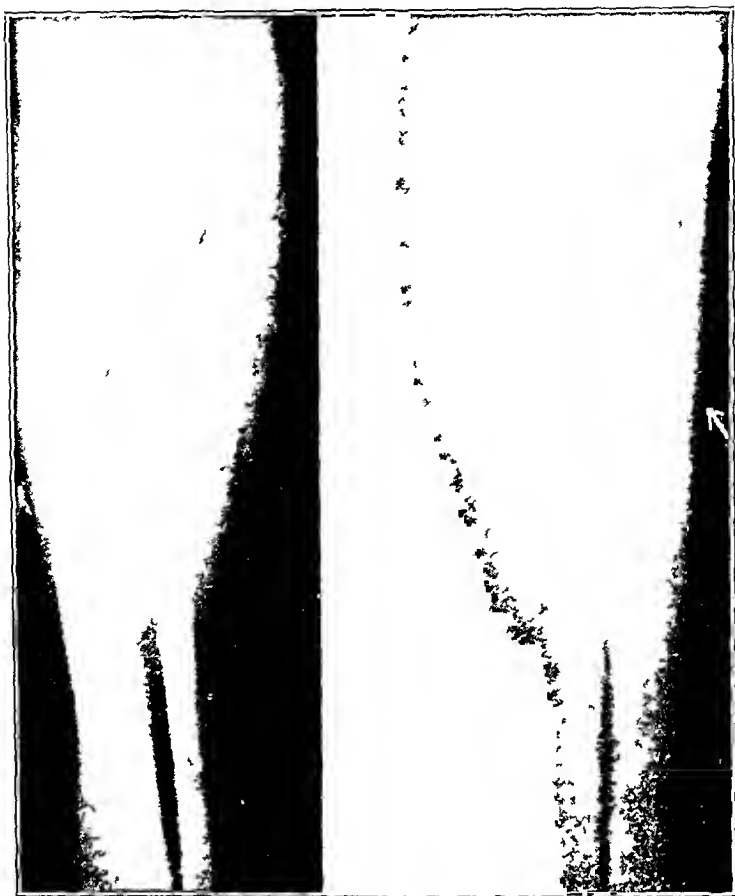


Fig 22 (case 5) —Roentgenogram taken seven weeks after the flap operation showing more complete union of the tibia with periosteal proliferation. The roentgenogram is dark because of efforts to show up the periosteum.

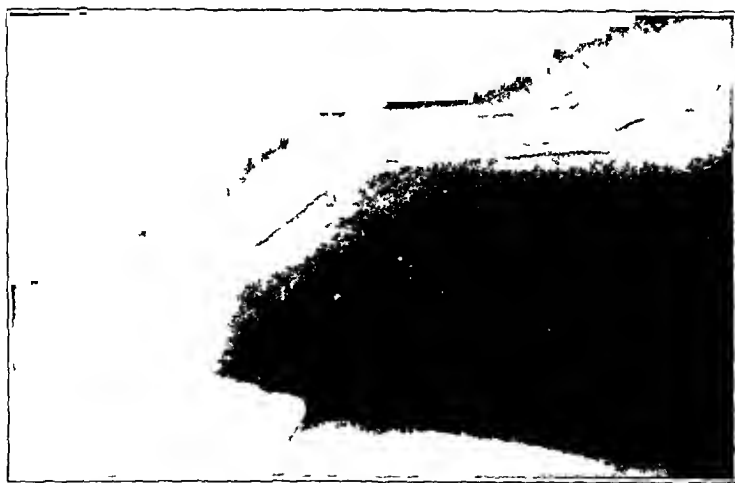


Fig 23 (case 6) —Roentgenogram taken before operation showing nonunion and marked atrophy of the bone.

A roentgenogram showed a slight deformity of the shaft due to the fracture of the step-cut, but the periosteal callus, which made its appearance early, undoubtedly saved this patient many weeks of invalidism by its fixative properties

CASE 7—M, a colored man, suffered a fracture of both bones of the forearm, the lower third of the radius and the upper third of the ulna. The radius was well reduced, but the ulna had been left in poor position and had not united. Eight weeks after the original reduction, there was no bony union in the ulna, although the radius was firm.



Fig 24 (case 6) —Roentgenograms, lateral and anteroposterior views, taken two weeks after operation showing marked periosteal deposition and a fracture of the step-cut of the lower fragment

At operation a periosteal suture was inserted after the bony fragments had been well opposed.

A roentgenogram taken one week after operation showed the fragments to be in good position.

Comment—From the foregoing experimental work and the clinical cases in which operation has been performed so far, it would seem that

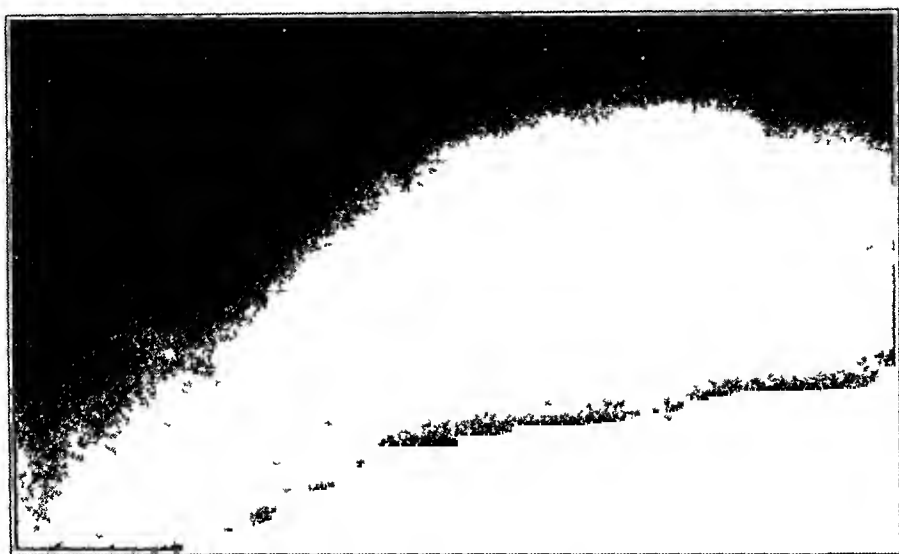


Fig 25 (case 6) —Roentgenogram taken four weeks after operation showing heavy periosteal, with beginning endosteal calcification

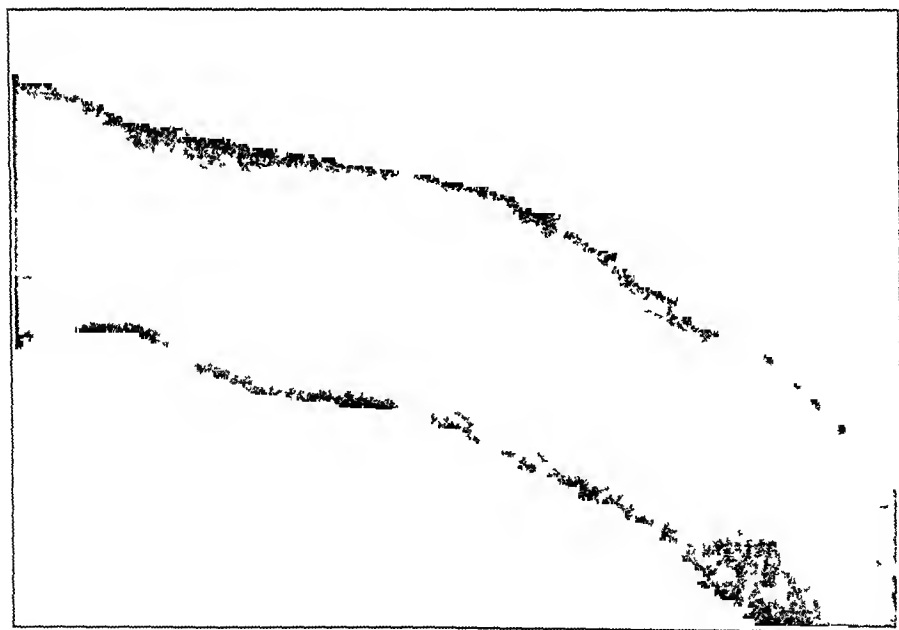


Fig 26 (case 6) —Roentgenogram taken five weeks after operation showing union progressing well, and good alinement of the bones

the rôle of the periosteum as a suture offers a fertile field for investigation. All the properties of this tissue have not been fully utilized, and the various researches which have been done on bone repair have largely attempted to prove the relative value of endosteal and periosteal callus. It is not contended that the periosteum itself is the curative agent for fractures, for unquestionably the only permanent and strong repair comes through the channels of endosteal or medullary callus, but this

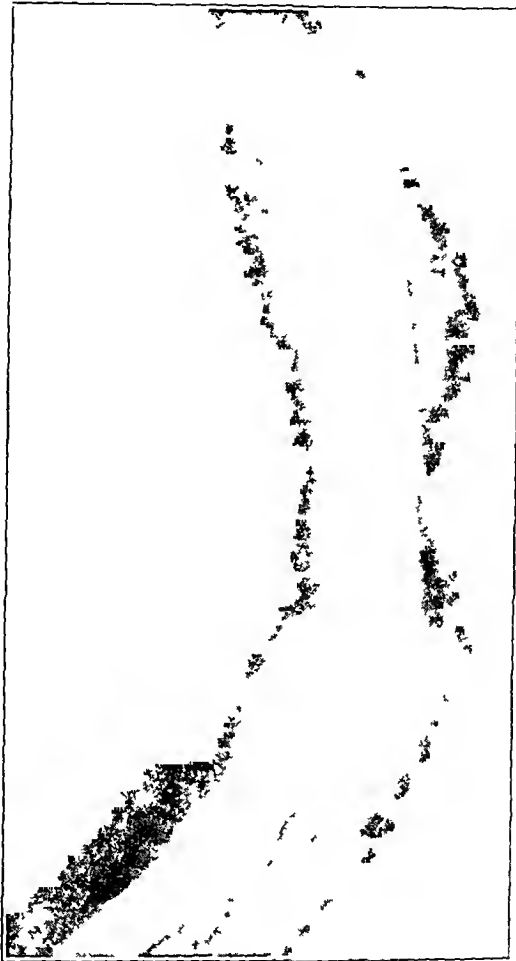


Fig 27 (case 6) —Roentgenogram taken six weeks after operation showing union complete and firm by both periosteal and medullary callus. There is much less atrophy of the bone.

is relatively late in its appearance, and the necessity of a strong, non-irritating, noncirculatory disturbing suture for the purpose of producing an early fixation can readily be appreciated, even though the periosteal blood supply penetrates but a short way into the cortex. According to Johnson, this must be of material aid in early repair of fractures.

One must recognize and differentiate between early and late repair. The suture alone cannot be depended on. All the other well accepted

methods of treating open reduction should be strictly adhered to, such as proper aseptic technic, proper immobilization in splints or plaster and early physiotherapy in order to stimulate the blood supply further

It is not argued that the use of periosteal suture should be universal and applied to fractures of all the long bones. One should select the cases with care. Periosteum is certainly not strong enough to hold firmly in fractures of such bones as the femur or the tibia in large persons, but it is most applicable to those fractures of the radius and ulna which resist one or two attempts at closed reduction and those of the humerus in which some internal fixation is necessary. In other words, the periosteal suture would seem to apply well to fractures of the long, nonweight-bearing bones. Its use seems most desirable in those cases, because fractures of the arm and of the forearm always bring to the fore the question of ultimate utility in the joints adjacent to the affected parts. Surgeons can appreciate the necessity for early mobilization of the wrist joint, the elbow joint and the shoulder joint, but frequently one is in a dilemma and fears to start motion in these joints because of the dangers of displacement. If the callus of a periosteal graft occurs as early as it appears to, one may start physical therapy at an earlier date than that ordinarily attempted in practice, for though the bones may tend to bend at the site of the injury, there is sufficient internal fixation by living osteogenic tissue to prevent a complete displacement of the fragments. Periosteal suture seems to have the further advantage that if such a displacement should occur due to an inefficient splint, one can readily reoppose the displaced fragments under the fluoroscope, still leaving the periosteal graft intact.

CONCLUSIONS

- 1 Autogenous periosteum has a definite tensile strength which does not vary when it is brought into contact with free body fluids
- 2 It is easily obtained from the broad, anterior surface of the tibia
- 3 If care is taken in the removal of the periosteum to elevate the small particles of the outer layer of the cortex, it is definitely osteogenic when placed in contact with cortical bone
- 4 Periosteum proliferates best when the grafted bone is thoroughly immobilized
- 5 Its proliferation in immobilized bone is rapid and early
- 6 It does not interfere with the circulation in the fragmented ends, but rather increases the circulation of this region, thereby offering an aid to the formation of late callus
- 7 The use of the periosteal suture allows mobilization of the fractured extremity at an early date

The silver impregnation method, a differential stain for calcium salts, has been recently devised by Dr Lillie of the Hygienic Laboratory, Washington, D C Dr Lillie has been of invaluable assistance in studying the microscopic sections of the experimental work

The roentgenograms and prints were all made by Mr Robert Brown of the Emergency Hospital X-ray Department Dr McPeak, roentgenologist of the same institution, supplied all of the rabbits and clinical cases in which roentgenograms were made

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A ONE-STAGE COMBINED RESECTION OF THE RECTUM

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A good surgical operation is conceived in an understanding of the origin and method of dissemination of the disease. It is an attack that is well planned with knowledge of the anatomy involved and with the expectation of a morbidity and mortality reasonably small in relation to the relief that ensues. To the degree in which these fundamental conditions are fulfilled does the operation approach the ideal. In the light of new contributions to the knowledge of both normal and pathologic anatomy and physiology, one must at intervals reevaluate one's surgical procedures. In so doing one learns why methods once thought to be theoretically sound have proved unsatisfactory in practice, and one may plan for the future on a more certain basis of fact.

The surgery of carcinoma of the rectum was for many years in the hands of two diametrically opposed groups, the Germans holding to the posterior approach and the French to the combined abdominal and perineal, the American and English tendency was rather in favor of the combined procedure. But information of outstanding practical value was reported by Miles in 1920, and by Villemain, Huard and Montagne¹ in 1925, on the lymphatic drainage of the rectum. They demonstrated that the channel of spread from the upper part of the rectum (above the last valve of Houston) is toward the abdomen, and that the channel from the lower part of the rectum is largely downward, but in part to the groin and abdomen. This work was reviewed in a masterly discussion of carcinoma of the rectum by Pfeiffer.² He postulated five points on which there is general agreement by the proponents of both the combined and the posterior operations.

1 In spite of the many instances of low malignancy and late metastasis observed in cancer of the rectum, permanent cures have increased in number, *pari passu* with wider ablation of related tissue.

2 There is no debate concerning the liability to metastatic involvement of the upward zone of spread in a certain percentage of cases.

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1 Villemain, Huard, and Montagne, quoted by Pfeiffer (footnote 2)

2 Pfeiffer, D. B. *Ann Surg* 76:374, 1927

3 From the sole standpoint of cure, therefore, there is excellent reason for including this area in the bloc to be removed

4 In most cases, complete removal of this area can be carried out only by the aid of previous intra-abdominal mobilization

5 Those who do not practice consistent and complete removal of this zone limit their procedures for other reasons than those which have to do with permanent cure, *e g*, mortality, morbidity, wider applicability, less frequent necessity for abdominal anus and a feeling that their results are practically as good

The consideration of these points has led most American surgeons of wide experience to adopt a combined operation, such as the Jones or Coffey procedure, as giving the best chance of cure. An operation the abdominal stage of which consists only of exploration and colostomy without mobilization of high lymphatic-bearing areas for subsequent removal from below cannot be considered to fulfil the requirements of the combined operation. Jones, while advocating the use of operations suitable to the strength of the individual patient, said³ "If we confine ourselves to an operation which can be used even on the feeble, we are not doing justice to those who can stand a more extensive operation." The newer knowledge of the lymphatics explains the observation that operations from below do not always afford sufficiently high dissection, an added indictment to the too frequently occurring terminal gangrene of the bowel, paralysis of the bladder, osteomyelitis of the sacrum and sacral hernia, chargeable to the Kiaske operation and its modifications. As surgeons have familiarized themselves with the technic of the combined operation, they have tended to do it in one stage. This is desirable from the point of view of technic, since it avoids the occasional "blow-outs" occurring after the first stage. Equally important, since it applies to every patient, is the lowering of morbidity with considerable saving to the patient's purse and morale. We cannot agree with the statement that high morbidity is of no consequence in dealing with cancer. We believe that it is of considerable importance to elderly patients whose chance of living for three years has only recently risen to 50 per cent under the most favorable circumstances. The present combined operation, when done in one stage, is a long one in the best of hands, and will carry a considerable mortality in the practice of those who are called on to do it only infrequently. The chief cause of the difficulty and consequent slowness of the one-stage procedure lies in its fundamental procedure of performing the most difficult part of the abdominal stage, the deep pelvic dissection, with the rectum and anus intact. We propose to reverse the entire procedure, and by first freeing the lower segment, vastly simplify and shorten the mobilization of the structures reached through the abdomen.

³ Jones, D F. *Ann Surg* 90 675, 1929

Before proceeding to the particulars of technic, we shall touch briefly on colostomy as a preliminary step. Reports by Rankin on large series of cases of tumors at all levels in the large intestine have shown the striking reduction in mortality and the extension of operability accomplished by colostomy and the institution of a definite regimen for the rehabilitation of certain patients. We are not committed to preliminary colostomy in all cases of cancer of the rectum and rectosigmoid. In this respect, patients are classified into three groups. At one extreme are those whose general condition is good and who do not need colostomy. Opposed to these is the group who must have colostomy because of obstruction, fixation of tumor or general depletion from pain, hemorrhage or infection. Between these extremes lies the group of patients whom one may or may not decide to explore with incidental colostomy on the suspicion of metastases to the liver or the peritoneum because of generalized tenderness or suspected free fluid. An argument in favor of preliminary colostomy in all cases is that if one performs it on a patient in whom there seems to be no necessity for it, the deferring of resection for three or four days is apt to be repaid several-fold by one's freedom to leave a clamp on the intestine much longer after resection, allowing complete primary union of the larger incision through avoidance of fecal phlegmon. We feel that attempts at extensive exploration, particularly of a site at which subsequent operation is to be performed, do not repay us in the degree to which they render more difficult the later procedure. Therefore, in the presence of infection in a rectal cancer with its well known effect on the regional lymph nodes and on the tumor itself, we look largely to the upper part of the abdomen for evidence of more than local metastasis.

When preliminary colostomy has been decided on, instead of the usual opening in the descending or sigmoid colon we make a fecal fistula in the ascending or transverse colon, since here, through the smallest opening, one can palpate the liver and detect carcinomatosis of the peritoneum and free fluid. With the colostomy placed high on the right side, the subsequent operation is performed through an abdominal wall on the pelvic colon and peritoneum undisturbed by previous manipulation and free from adhesions other than those of the disease itself. The contents of the ascending colon being largely fluid, we do not need to bring a loop of bowel outside the abdominal wall, but on these patients we perform a rapid and shockless enterostomy which differs from that employed for acute obstruction only in its location and accompanying exploration. If the diagnosis has been made previously, the colostomy is performed on the day of the patient's admission to the hospital. Its technic is as follows:

TECHNIC OF COLOSTOMY

Phenobarbital, 15 grains (0.97 Gm), is given three hours before operation (unless the patient has acute obstruction and is vomiting). Under nitrous oxide, a vertical incision from 6 to 7 cm long is made well within the lateral border of the right rectus. If the liver cannot be percussed below the rib margin, the upper limit of the incision should be made to within 1 cm of the rib. The incision is carried down to the posterior sheath and the peritoneum, which are opened only enough to introduce an exploring finger. The liver may be palpated, the visceral and parietal peritoneum visualized to a limited extent by manipulation and any gush of free fluid detected. If the colon is not readily identified and brought up to the peritoneum, the incision in the posterior sheath and the peritoneum is extended to the limit of the skin incision, and the location of the colon is more readily carried out. The intestine is grasped in an Allis clamp, which is carried to the upper angle, and the peritoneum and posterior sheath are closed to within 1 cm of the upper angle. Retraction directly upward on the Allis clamp brings the wall of the intestine into the small opening remaining in the peritoneum, to which it is fixed by four interrupted sutures of 0000 silk, such as we use for closing goiter incisions, leaving the needle on the last suture. The entire incision is then flooded with 95 per cent alcohol, and the intestine is incised just enough to admit a guttered semistiff rubber tube, 1 cm in diameter, which is inserted to a distance of 5 or 6 cm and transfixed with the last suture used on the intestine. The tube is cut off 2 cm beyond the level of the skin. No sutures or dressings are used. The stitch holding the tube may be cut after three or four days or be allowed to cut through.

We have not yet had to do a secondary closure after an enterostomy performed by this technic. After a period of about ten days a Pezzar catheter is inserted into the intestine and may be worn as long as it is desired to keep the fistula open. The incision closes in rapidly, and we have had such tubes in place on three different patients at the same time, all of them keeping entirely watertight. The tube may be clamped off as desired to test the patency of the intestine below. At the present writing, one of our patients, a woman, has worn such a tube for four months, with complete comfort. The location of this incision varies somewhat with the habitus and previous intra-abdominal history of the patient. Since the transverse colon is so variable in location in the absence of intra-abdominal disease, and is usually drawn down by former appendicitis or upward by cholecystitis, judgment must be exercised as to whether one should make a high rectus incision, as here described, or a muscle-splitting incision lower down to pick up the ascending colon. The main requirement is that one reach the colon as near the liver and as far from the field of subsequent operation as possible.

The interval between colostomy and resection is regulated entirely by the patient's condition. Patients with obstructions, and depleted or bled-out patients must be fully restored. Transfusions of blood are invaluable for patients not in normal condition for any reason. Cleans-

ing of the bowel by irrigations, so far as it can ever be accomplished, takes only a few days in conjunction with a residue-free diet. We have noticed that attempts to wash the colon through a high colostomy are often unsuccessful with saline solution, owing to its absorption en route, tap water, of course, goes through readily. To the fruit juice and candy diet suggested by Rankin and Baigen, we add tea, coffee, juices of canned tomatoes and sauerkraut, fruit ices, malt tonic (containing 2 per cent alcohol) and any other alcoholic beverages, since the patients are usually elderly. Following resection, it is important that this diet be continued until the clamp has cut through.

When the patient's condition warrants, resection is carried out according to the following technic:

TECHNIC OF RESECTION

Phenobarbital (15 grains) is given three hours before operation (a smaller dose, or none at all, is used if the patient is very thin or old, or has a low blood pressure). If a fecal fistula is present, it is packed and covered. The patient is placed in a "broken-V" face position on the table, both the head and the feet being low. He is draped and prepared for the perineal stage, after all preparation is complete, the upper part of the draping is lifted and held away so that a spinal anesthetic may be inserted into the second or third lumbar interspace. After the injection of the anesthetic, the spinal needle is left in place, its stylet inserted to prevent further flow of spinal fluid, and a small soap dish or wire cage fastened over it to prevent change in its position during the course of the operation. The drapings are returned to place. The rectum is packed with iodoform gauze (1) to be used as a mold or cast for identification and (2) to prevent spilling of rectal contents in case of accidental injury. The skin around the anus is cut in a circle and sutured over with a continuous stitch. The incision is continued posteriorly in the midline up to the sacrococcygeal joint, and the coccyx is removed. The steps of the typical posterior operation are then performed, the lowest portion of the sigmoid is released by opening the peritoneum. A wide, soft rubber tube, such as would be made by closing a Penrose drain at one end, is then drawn over the specimen and anchored high up with a few sutures for the sake of safety (fig 1). This rubber-covered mass is gently pushed up into the peritoneal cavity. The entire defect thus created is loosely packed with iodoform gauze after the necessary ligations have been made, no stitches being taken anywhere, and a large dressing is applied. The drapings are removed, the stylet is withdrawn from the spinal needle, and the patient is told to cough to ascertain whether the needle is still within the dura. A second dose of the spinal anesthetic is given, following which the needle is withdrawn. This insures one against having to use inhalation anesthesia, even though the operation takes longer than the calculated time. The patient is turned on his back and placed in the Trendelenburg position, the abdomen is opened widely from 1 to 2 cm to the left of the midline from the pubis to the umbilicus. The tumor mass is retracted out of the abdomen and is held toward the ceiling until the conclusion of the operation (fig 2). The customary division of the mesosigmoid is made at its attachment to the posterior wall of the pelvis and the lowest portion of the abdomen. Gross division of the mesosigmoid from the bony wall to the bowel is made at the usual point, and the upper sigmoid is drawn firmly into the upper angle of the abdominal incision.

The posterior peritoneum is completely closed, beginning with that portion first opened while the rectum was being freed from below. The abdominal wall is closed in layers without drainage, all layers are sutured as snugly as possible around the sigmoid without risking necrosis, no stitches being placed in the bowel. A rather heavy rubber-covered clamp is placed across the intestine 1 cm from the skin, and 1 cm beyond the clamp the sigmoid is cut through with the cautery, after the wound has been covered with petrolatum of the highest melting point, which is constantly renewed by the nurse during postoperative care. A wire cage protects the whole operative region, no dressings are used for fear of capillary

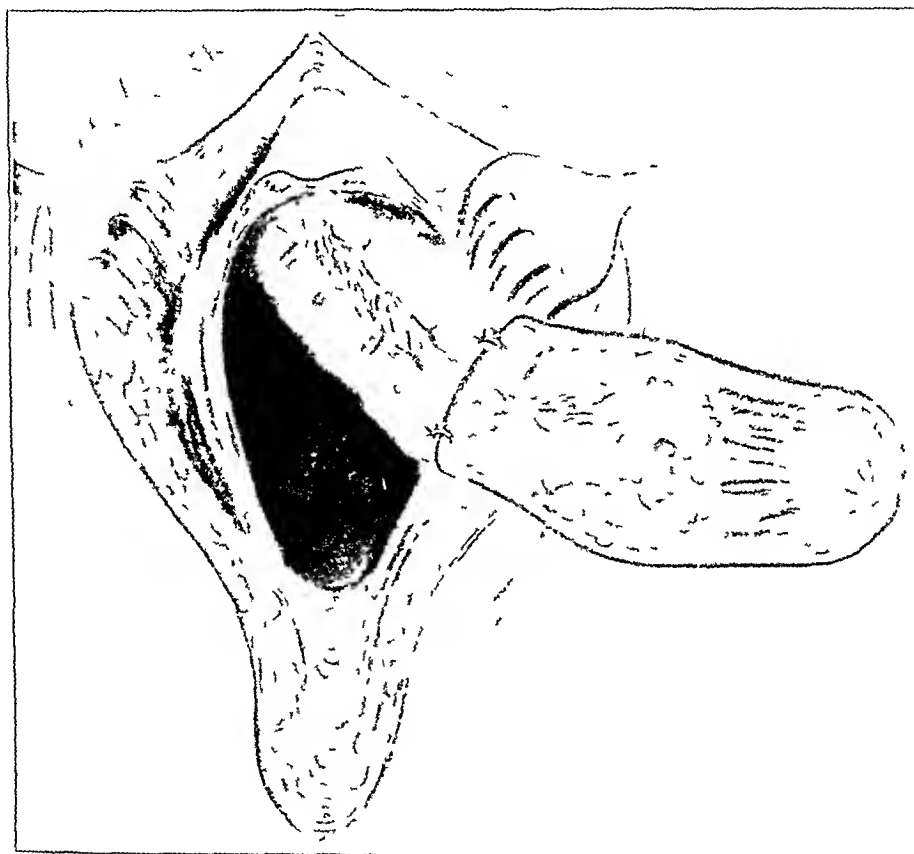


Fig 1—Dissection completed from below. Specimen covered with rubber

drainage and soiling from fecal fistula, if this has been formed, or from permanent artificial anus when the clamp has cut through after several days.

This method of resection was first used, without premeditation, on a man on whom the posterior operation was being performed, as it had been decided that the cancer was too far advanced to make the combined operation worth while. His tumor was found to have canalized the rectum and to have extended so high that it could not be removed from below. The blood supply had already been sacrificed, and the best way out of the dilemma was to push the mass up into the abdomen and to

complete the operation from above. A short abstract of the history of this patient and that of a second one on whom this operation was performed are as follows:

REPORT OF CASES

CASE 1—J. J., aged 37, a salesman, complained of the frequent passage of blood from the rectum during and between stools and occasional profuse diarrhea,



Fig. 2.—Patient in Trendelenburg position. Specimen delivered through abdominal incision and kept on traction.

the history of the condition dating from a fall. Examination showed an irregular nodular mass, ulcerated and bleeding, situated $3\frac{1}{2}$ inches (8.9 cm) above the anal orifice on the posterior rectal wall; there were tender, slightly enlarged inguinal glands. The patient entered the hospital on Nov. 9, 1924, and was operated on four days later under spinal anesthesia; the packing was removed on the second day, and patient was discharged on the sixteenth day with the abdominal incision healed but the rectal defect not yet fully granulated in. Four months later he had gained 15 pounds (6.8 Kg) and was feeling excellent but three months

after this he contracted influenza, during which he lost 12 pounds (5.4 Kg), he returned for observation shortly afterward complaining of pain in the right lower quadrant and hard masses in both groins. He died a few months later.

CASE 2—H. S., aged 41, a clerk, complained of soreness in the rectum, especially with bowel movements, slight intermittent bloody discharge and pencil stools for six weeks preceding observation. He had been treated for hemorrhoids. He had lost 8 pounds (3.6 Kg) in two months and had had some dysuria for three weeks. Examination showed a hypertrophic, ulcerated, hard mass, 3 inches (7.6 cm) in diameter, which bled readily, located 3 inches from the anal margin on the posterior rectal wall, largely to the left of the midline. There was considerable accompanying proctitis. An abdominal examination yielded negative results. The patient entered the hospital on Oct. 4, 1927, and was given a low residue diet and rectal irrigations. An operation was performed on October 11, and the pathologic report showed colloid carcinoma. The clamp was removed on the second postoperative day, the patient was allowed to sit up on the fourteenth day and thereafter, but his discharge from the hospital was delayed for nearly another month because of infection in the abdominal incision. His weight had returned to normal within two months after the operation, and shortly afterward he returned to work. Six months after operation he complained of pain in the buttocks and thighs, but had not lost any weight. He died of metastases a few months later.

SUMMARY

Repeated spinal anesthesia may be used in this method. By liberating the rectum and anus and bringing them, enclosed in a rubber bag, out of the abdominal wound to be used as upward traction, the most difficult part of the operation, deep pelvic dissection, is greatly simplified, since the mesosigmoid is thrown into relief and put on the stretch. It is infinitely easier to work from the depths toward oneself than in the opposite direction. Higher division of the sigmoid may be carried out, and the superior hemorrhoidal is cut at a safe point. The posterior attack is shortened, there are no drains or tubes anywhere and there is no risk of a "blow-out" below the peritoneal closure. One may perform a preliminary colostomy for exploration, for relief from obstruction, for washing out the bowel and to enable one to leave the clamp on the intestine indefinitely after resection. With the fecal fistula made in the right upper quadrant, one can perform an adequate exploration and at a subsequent operation work in an abdominal wall and pelvis undisturbed by previous recent manipulation.

Jones wrote of the abdominoperineal operation: "The third objection to the operation, the length and difficulty of it in some cases, must be admitted, and only those who are willing to accept these conditions as part of the operation should undertake it." If, as we believe, the operation here presented advances us further along any of the lines fundamental to ideal operations, it will make a sound principle available to practice in the hands of a larger number of surgeons than formerly.

SARCOMA OF THE ESOPHAGUS ~

HAROLD J DVORAK, M.D.

MINNEAPOLIS

Carcinoma of the esophagus constitutes 50 per cent of all lesions of the esophagus (Abel¹) Sarcoma, on the other hand, is a rare condition (Ewing,² Kaufmann, Aschoff, Fischer³) Recently, there came under my observation a patient with such a lesion, and I therefore feel justified in reporting the case

REPORT OF CASE

History—Mrs R. T., a white woman, aged 27, was admitted to the University Hospital on June 11, 1927, complaining of epigastric pain, diarrhea and constipation Since March 8, 1927, she had suffered considerably with a burning epigastric pain which radiated to both sides of the thorax and up into the axillae, especially to the left The pain had been present almost daily, and it usually lasted from one-half to six hours She belched considerable gas and passed much flatus, but without relief There was no qualitative or quantitative food distress The pain often bothered her at night She complained of being "nauseated" more or less constantly, but vomited only on three different occasions, a greenish material She frequently missed breakfast because of the "nausea," otherwise, she ate well During the past three months she had lost 5 pounds (2.3 Kg.) Since the onset of her illness in March, she had also been troubled with attacks of diarrhea alternating with periods of constipation She had eight or ten such alternate attacks During the periods of diarrhea her bowels moved from three to four times a day The stools were soft, but not watery No blood or mucus was present She also said that she became easily excited and nervous and trembled frequently, her heart would pound on such occasions

In 1923, the patient was treated for an "ulcer of the stomach," apparently because her stools were black and tarry At this time she did not have any epigastric symptoms No roentgen examinations were made

In 1924, the patient gave birth to a normal living child There was no other pregnancy

In 1926, she said, her stools again became black Her physician told her that she had an ulcer of the stomach At that time, she had vague epigastric pains and heart burn from three to four hours after meals, relieved by the taking of food She had some nausea, but did not vomit She was put on a diet for several weeks There was no loss in weight, and her appetite was good She has not noticed black stools since then

* Submitted for publication, July 3, 1930

~ From the Department of Surgery and the Cancer Institute, University of Minnesota

1 Abel, A. Lawrence Oesophageal Obstruction, London, Oxford University Press, 1929, p. 160

2 Ewing, James Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1928, pp. 277 and 907

3 Fischer, Walther, quoted by Henke, F. and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 4, part 1

During the past year she felt very weak and nervous and tired easily, until March 8, 1927, when she first noticed the symptoms already mentioned. There was no family history of malignancy and no history of venereal disease. Her dietary and hygienic habits were good.

Physical Examination—Examination revealed a well developed and well nourished white woman, aged 27, lying quietly in bed. Her weight was 102 pounds (46.3 Kg). The skin was warm and moist. Her eyes, ears and nose were normal. The tonsils had been removed. The thyroid was soft and moderately enlarged. There was a slight systolic bruit over it. Slight enlargement of the

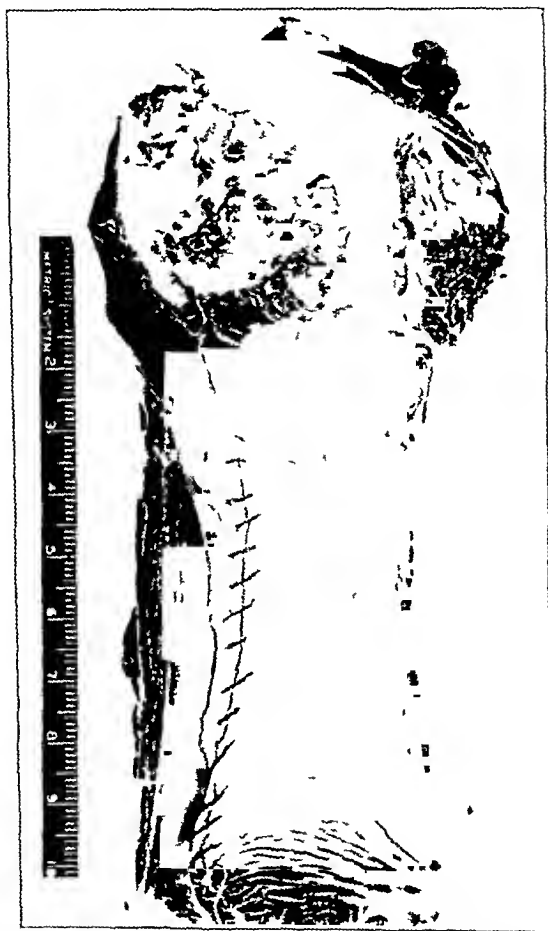


Fig 1—Rhabdomyosarcoma of the esophagus. The tumor was soft, polypoid, yellowish white, sharply circumscribed and from 4 to 5 cm in diameter. It sprang from the left anterolateral wall, about 5 cm below the pharyngo-esophageal junction. It bulged into the lumen and onto the external surface of the esophagus. The latter was sutured where accidentally cut.

cervical lymph nodes was present. The lungs and heart were normal. The blood pressure was 120 systolic and 78 diastolic, the pulse rate was 124. The abdomen was normal. Examination of the upper extremities on extension showed a coarse tremor of the fingers. The knee jerks were hyperactive. The basal metabolic rate was plus 25. The urine and blood were normal. Examination of the stools did not reveal blood macroscopically, microscopically or chemically. A gastric analysis gave normal results. The blood urea nitrogen and blood sugar were within normal limits. The Wassermann reaction of the blood was negative.

A diagnosis of hyperthyroidism was made. The patient was put on a compound solution of iodine, and given deep roentgen therapy to the thyroid gland.

On June 24, 1927, a roentgen diagnosis of a small prepyloric nonobstructing ulcer was made, and the patient was put on a Sippy diet. However, a roentgen examination made on July 16, 1927, failed to confirm the presence of the ulcer. Beginning on July 25, 1927, for several days she vomited her food immediately after eating. No definite cause could be found.

The patient was discharged from the University Hospital on Sept. 7, 1927. She had gained 15 pounds (6.8 Kg.), her basal metabolic rate was now minus 1 and she felt much better. She was advised to return later for further observation.

She was readmitted on Nov. 15, 1928, and said that she had felt well for some time after her discharge in September, 1927. In March, 1928, however, she had suffered a recurrence of the symptoms of a peptic ulcer. She was again put on

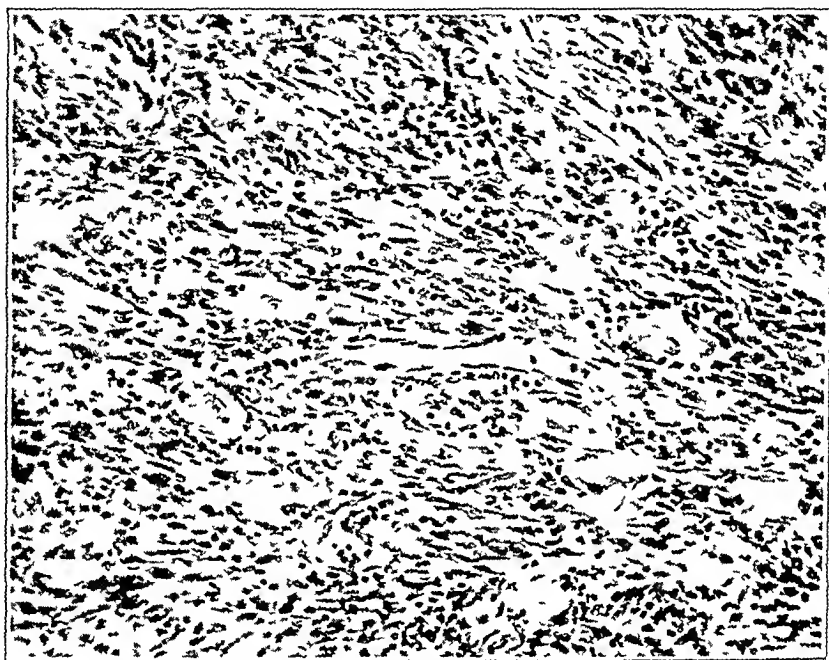


Fig. 2—Photomicrograph of figure 1. This shows masses of spindle cells and occasional giant and muscle cells. Hematoxylin and eosin, $\times 90$.

an ulcer diet and obtained immediate relief. However, slight pain in her stomach continued. It did not follow meals at regular intervals, but was relieved somewhat by eating and drinking. Sometimes the pain awakened her at night. Her appetite was good, and she ate all types of food. In March, 1928, she also noticed occasional gripping pains in the upper substernal region and base of her neck, and feelings of pressure in her throat, which she attributed to an ingrowing goiter. These symptoms persisted with more or less severity.

Second Examination—This showed a well nourished young woman with negative ocular signs and moist skin. There was a coarse tremor of her fingers on extension. Other physical observations were negative. The basal metabolic rate was minus four. The blood and urine were normal. The Wassermann reaction of the blood was negative. On Nov. 26, 1928, roentgen examination of the esophagus after ingestion of a thick barium paste was negative both by fluoroscopy and on the films. It was now believed that her symptoms were not due to hyperthyroidism, although they were similar to those presented on the first

admission. She was discharged at the end of November, with a diagnosis of functional esophageal or laryngeal spasm.

On Aug 12, 1929, she was readmitted to the hospital for the third time, and was assigned to the cancer department of Dr A C Strachauer. After the patient's discharge from the hospital in November, 1928, the tight feeling in her throat, located at the level of the jugular (interclavicular) notch, grew worse. In May, 1929, she first noticed difficulty in swallowing. By July 15, 1929, she was unable to swallow anything. During the six months previous to that time she had lost 40 pounds (18.1 Kg) in weight. Her family physician passed a stomach tube, and blood was withdrawn. The patient was admitted to the Abbott Hospital in Minneapolis, where an esophagoscope was passed by Dr Kenneth A Phelps. A tumor was found. Biopsy was made, and the lesion was diagnosed as spindle cell sarcoma with giant cells. Gastrostomy was performed at the Abbott

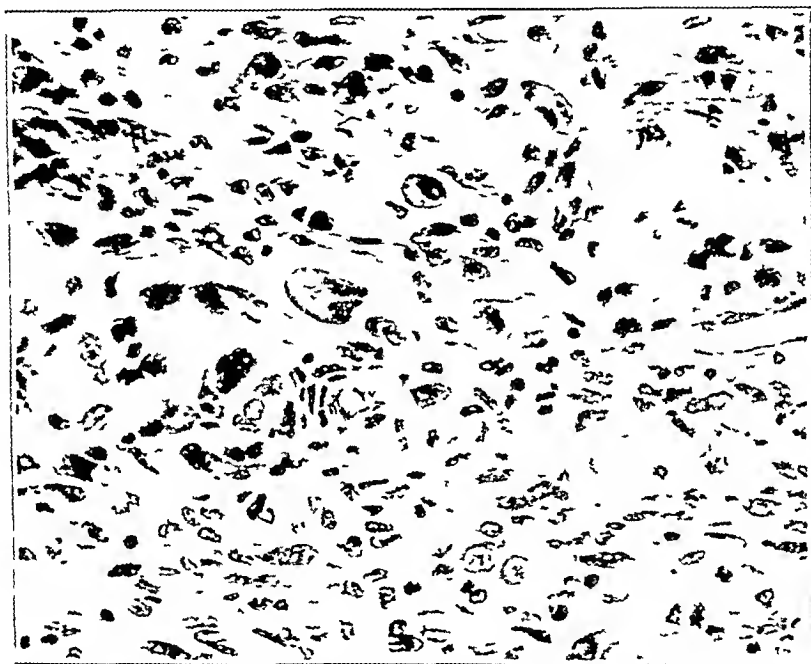


Fig 3—Higher power magnification of figure 2. Hematoxylin and eosin. $\times 250$

Hospital, and the patient was directed to the University Hospital for radiation treatment, where she now presented herself. Dr Phelps examined the patient again on admission here, and described the lesion as follows: "There is a large necrotic tumor mass which bleeds easily and appears to spring from the left anterior esophageal wall 20 cm from the incisor teeth, causing about 75 per cent obstruction of the lumen of the esophagus. The mass is partially covered by a white membrane."

Improvement in nutrition followed the gastrostomy, and the patient gained some relief from difficulty in swallowing. The blood showed moderate secondary anemia with hemoglobin of 65 per cent, red blood cells, 3,500,000, white blood cells, 10,450, polymorphonuclears, 83 per cent, and lymphocytes, 17 per cent. A mass was now palpable on the left side of the neck at a level just below the larynx. Roentgenograms showed a malignant condition of the esophagus beginning at a level corresponding to about the second or third dorsal vertebra, or

about 5 cm below the pharyngo-esophageal junction, and extending downward for about 4 cm. The malignant process displaced the esophagus to the right, suggesting pressure by an extrinsic mass.

On Aug 22, 1929, 1,050 millicurie hours of radium were inserted into the mass by capsule through an endoscope. On September 25, a 105 per cent skin erythema dose of deep roentgen rays given in four treatments over eight days, was administered over the diseased area by Dr Karl W Stenstrom. Marked reaction with vomiting followed.

Her respirations became more labored, and her physical condition gradually declined. Toward the end she complained of a good deal of dyspnea. She died on November 20, probably of respiratory obstruction. It was felt that this could not be relieved because of the location of the growth. Radical extirpation of the growth was never considered, because it was believed that the lesion was extrinsic to the esophagus in origin and involved the latter only secondarily.

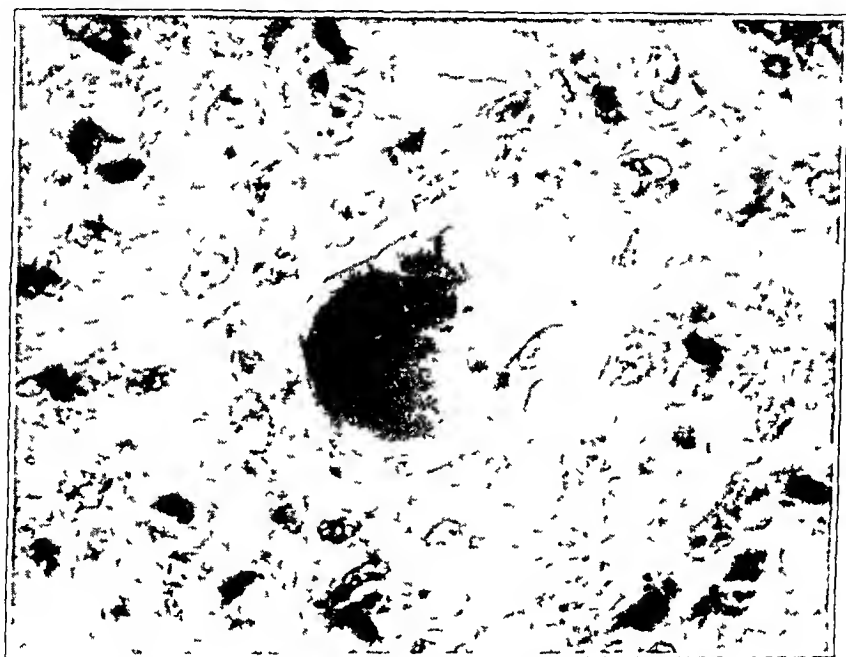


Fig 4—Higher power magnification of figure 3, showed a large muscle cell in the center of the field with nucleus and nucleoli. No cross-striations were demonstrated. Phosphotungstic acid stain, $\times 800$.

Necropsy—The postmortem examination, made by Dr William A O'Brien, associate professor of pathology, University of Minnesota, showed a well developed though emaciated woman. There was a gastrostomy opening present in the left upper quadrant of the abdominal wall. Five centimeters below the pharyngo-esophageal junction (lower edge of cricoid cartilage) there was a soft, yellowish-white, sharply circumscribed, polypoid tumor, from 4 to 5 cm in diameter, springing from the left anterolateral wall of the esophagus and bulging partly into its lumen and partly from its external surface. The latter observation gave rise to the previous belief that the lesion was extrinsic, and only secondarily infiltrated the wall of the esophagus. It did not penetrate the tracheal wall, though the latter appeared slightly discolored black on its internal surface, probably from pressure. The rest of the organs were normal. There were no metastases. The para-esophageal lymph nodes were not even visibly enlarged. The lesion appeared operable.

Histologic study of the tumor under the direction of Dr E T Bell, professor of pathology at the University of Minnesota, showed the constituents of the tumor to be predominantly spindle cells, some multinucleated giant cells, some round cells, fibrous connective tissue and a liberal sprinkling of muscle cells. The blood supply was moderate. The spindle cells occasionally showed mitotic figures. The muscle cells were very large, oblong or rectangular or when seen in cross-section round. The nuclei were relatively small, oval, dark staining and usually eccentrically placed. Special phosphotungstic acid stains showed a massive pink staining cytoplasm with longitudinal fibrillations. Cross-striations could not be demonstrated. This was attributed to failure of fixation of the fresh tumor tissue in the proper solution. Nevertheless, it is believed that these embryonal cells were differentiating into striated muscle of the voluntary type. The diagnosis was rhabdomyosarcoma of the esophagus.

Glinski⁴ and others have shown that cross-striations in the muscle cells of these tumors are frequently difficult to demonstrate, and often cannot be found. This is especially true when the tumor process is very undifferentiated.

DISTRIBUTION AND INCIDENCE

Distribution of Sarcoma in the Digestive Tract—Corner and Fairbank⁵ studied 175 cases of sarcoma of the alimentary canal. Of this number, 14 occurred in the esophagus, 58 in the stomach, 65 in the small bowel, 20 in the cecum, 11 in the colon and 7 in the rectum.

Number of Cases in the Literature—Chapman⁶ (1877) was the first to describe esophageal sarcoma. Starck⁷ (1900) collected seven cases and added two. Hacker⁸ (1909) collected twenty-one cases. Hacker and Lotheissen⁹ (1926) said that only thirty-eight had been described, and in some of these the origin was doubtful. Among the thirty-eight were three cases which arose mostly from the hypopharynx and only to a small extent from the esophageal entrance. Walther Fischer³ (1926) found about fifty reported cases. Simon¹⁰ (1928) said there were only thirty objection-free cases in the literature.

4 Glinski L K. Ueber polypenformige Mischgeschwülste des Oesophagus. Virchows Arch f path Anat **167** 383 1902.

5 Corner M, and Fairbank H. Sarcomata of the Alimentary Canal, Lancet 1904 p 1503.

6 Chapman S H. Sarcoma of Interior Constrictor of the Pharynx and Inlet of the Oesophagus. Am J M Sc **74** 433 1877.

7 Starck Hugo. Sarkome des Oesophagus, Virchows Arch f path Anat **162** 256 1900.

8 Hacker V. Zur Kenntnis des Oesophagus-sarkoms. Mitt u d Grenzgeb d Med u Chir **19** 306 1909.

9 Hacker, V, and Lotheissen G. Chirurgie der Speiseröhre in Neue deutsche Chirurgie Stuttgart Ferdinand Enke 1926 vol 34 p 368.

10 Simon Hermann. Die Sarkome in Neue deutsche Chirurgie Stuttgart Ferdinand Enke 1928 vol 43 p 246.

Age Incidence—The age distribution is as follows. Hacker and Lotheissen in their thirty-eight collected cases, found only one sarcoma a lymphosarcoma, in a very young patient. This was in Stephan's¹¹ case, that of a child aged 4. All the others occurred in persons between 32 and 84 years. In ten cases no age was given. Three patients were between 30 and 40 years, eight, between 40 and 50 years, seven, between 50 and 60, ten, between 60 and 70, one between 70 and 80, and one was 84 years old. Three hypopharyngeal cases occurred in patients aged 45, 64 and 64 years, respectively. Eighty-five per cent of all sarcomas occur in persons over 40 years of age, as is true also of carcinoma. However, sarcomas occur more frequently in the young than do carcinomas, the average age of occurrence being 55 years.

Sex Incidence—Though the sex was not always mentioned in the Hacker and Lotheissen collected series of thirty-eight cases, yet the occurrence among women was mentioned only six times. Seventy-eight per cent of the cases were among men. This observation is similar to that in carcinoma. Most authors agree regarding the relative infrequency of the condition among women as compared with men.

LEVEL OF PREDILECTION IN ESOPHAGUS

The tumor is found most frequently in the lower portion of the thoracic part of the esophagus, but gives more signs and symptoms in the cervical part. Like carcinoma, the points of predilection are usually at the level of one of the three esophageal constrictions. In thirty cases reported in the collected series of Hacker and Lotheissen the tumor arose only seven times in the cervical portion of the esophagus, the predilection being for the lower part of the thoracic portion, just a few centimeters above the cardia of the stomach. Only occasionally do they lie in the upper thoracic part of the esophagus, according to this author. These tumors can also arise in the upper part of the pharynx and can then grow down into the esophagus. In the same series were three cases in which the tumor arose partly from the esophagus and partly from the lower portion of the pharynx. Carcinoma, on the other hand arises most frequently in the middle third of the esophagus and least frequently in the upper third. Sarcoma, especially if it is of the circumscribed polypoid type usually arises from the anterior wall of the esophagus and from its submucosa (Hacker and Lotheissen,⁹ Fischer,³ von Eicken,¹² Kaufmann, Aschoff and Donath¹³)

11 Stephan B. H. Zur Kasuistik der Dysphagie bei Kindern (Sarcoma Oesophagie bei einem 4 Jahrigen Knaben), *Jahrb f Kinderh* 30 354, 1890

12 von Eicken Carl. Ein Sarkom der Speiseröhre, *Deutsche Ztschr f Chir* 65 380, 1902

13 Donath Kurt. Beitrag zur Kenntnis der sarkomatösen Geschwülste der Speiseröhre. *Virchows Arch f path Anat* 194 446 1908

GROSS MORPHOLOGY AND EXTENT OF PROCESS

Simon,¹⁰ Hacker and Lotheissen⁹ and Fischer⁸ classified sarcomas grossly on the following basis

1 The more circumscribed type These have a broad base overlaid with polyps with distinct pedicles sometimes even 16 cm long (Borrmann¹⁴) The polyps consist of nodules and excrescences springing forth into the lumen and are covered by a smooth mucosal surface These tumors are whitish or whitish yellow, hard or soft sometimes even gelatinous, and many times superficially ulcerated The size varies from that of an almond to that of a hen's egg They seldom involve much of the esophageal circumference and seldom cause stenosis

2 The diffuse infiltrating type These are very malignant and difficult to differentiate clinically from carcinoma They grow fast and form superficial ulcers which may be 14 cm long In individual places they can be more or less polypoid or cauliflower-like

Multiple sarcomas have been seen

Extent of the Pathologic Process—In Gastpar's¹⁵ case the lesion extended from the bifurcation of the trachea to the cardia of the stomach, and was both nodular and cauliflower-like Baur's¹¹ melanosarcoma started at the origin of the esophagus and extended 10 cm downward, perforating into the trachea Other tumors as in my case may be no larger than from 4 to 5 cm in diameter

HISTOLOGY OF ESOPHAGEAL SARCOMA

Ulcerative lesions usually contain round or polyhedral cells, the polypoid lesions, spindle cells Stephan's¹² case in a 4 year old child was a lymphosarcoma Secondary lymphosarcoma of the esophagus has been observed by Schlagenhauser¹⁷ Kaufmann said that lymphosarcomas are very rare and melanotic sarcomas most rare Hofmann¹⁸ described a pigmented spindle cell sarcoma, Baur a melanosarcoma Bertholet¹¹ reported a small round cell sarcoma derived from a lymph follicle

14 Borrmann R. Zwei polypöse Oesophagus Sarkome bei einem Individuum, Verhandl d deutsch path Gesellsch **12** 121 1908

15 Gastpar A. Ein Fall von Oesophagussarkom Centralbl f allg Path u path Anat **11** 81 1900

16 Baur E. H. Ein Fall von primärem Melanom des Oesophagus, Arb a d Geb d path Anat Inst zu Tübingen **5** 343 1904

17 Schlagenhauser Friedrich. Zwei Fälle von Lymphosarcom der bronchialen Lymphdrüsen mit secundärer Lymph Sarcomatose des Oesophagus, Virchows Arch f path Anat **164** 147 1901

18 Hofmann M. Zur Klinik der polypösen Sarkome des Oesophagus Beitr klin Chir **120** 201 1920

19 Bertholet E. Du sarcome de l'oesophage Arch d med exper et d anat path **23** 135 1911

Round cell sarcoma has also been described by Rolleston,²⁰ Staick,²¹ Wegener²¹ and Huismans²² Staick's two cases were of the large round cell type. These were not polypoid grossly and, therefore, truly malignant. Ewing said that many round cell sarcomas are nothing less than anaplastic carcinomas. Fischer stated that round cell tumors are probably either lymphosarcomas or embryonal, that is, undifferentiated, carcinomas. The spindle cell tumors are real sarcomas.

Hacker⁸ (1909) found in his collected series of twenty-one cases that more than half of the cases were of the round cell or mixed cell type, the latter of which contain round cells. These are more malignant than the relatively benign spindle forms and those containing muscle fibers. Reith²³ described two cases, predominantly of the giant cell type, von Lange,²⁴ a spindle and large round cell type, Hacker, primarily round and spindle cells. Mixtures of these cell forms were seen by Chapman, Gastpar, Shaw²⁵ and Targett²⁶. Howard²⁷ and Eppinger²⁸ saw, in addition to this content smooth muscle fibers. Rarely has genuine leiomyosarcoma as reported by Hacker and Bauer²⁹ been described.

Spindle cell sarcomas have been reported by James,³⁰ Livingood,³¹ Notthaft³² and Ogle³³. Tumors containing partly spindle cells, either large or small and partly giant cells, were described by Boimann,

20 Rolleston, H. D. Sarcoma of the Oesophagus with Secondary Growths in the Bone, *Tr. Path. Soc. London* **44** 65, 1893.

21 Wegener. Ueber das Sarkom des Oesophagus, *Inaug. Diss.*, Giesen, 1904.

22 Huismans, L. Sarcoma Oesophagi, *Munchen med. Wchnschr.* **48** 2147, 1901.

23 Reith, J. W. Ueber Zwei Falle von primarem Sarkom des Oesophagus, *Inaug. Diss.*, Leipzig, 1909.

24 von Lange. Primares Oesophagussarkom, *Munchen med. Wchnschr.* **51** 411, 1904.

25 Shaw, Lauriston. Sarcoma of the Oesophagus Perforating the Trachea, *Tr. Path. Soc. London* **42** 90, 1891.

26 Targett, J. H. Sarcoma of Oesophagus, *Tr. Path. Soc. London* **40** 76 1889.

27 Howard, W. T., Jr. Primary Sarcoma of the Esophagus and Stomach, *J. A. M. A.* **38** 392 (Feb 8) 1902.

28 Eppinger, quoted by Hacker (footnote 8).

29 Bauer, Ervin. Zur Kasuistik der Oesophagusmyome. Ein Beitrag zur Lehre der Myome. *Virchows Arch. t. path. Anat.* **34** 223, 1916.

30 James, G. B. Sarcoma of the Oesophagus with Secondary Deposit in the Tongue. *Tr. Path. Soc. London* **49** 91, 1898.

31 Livingood, L. E. A Case of Sarcoma of the Esophagus, *Bull. Johns Hopkins Hosp.* **9** 159, 1898.

32 Notthaft, A. Mors subitanea durch Platzen einer varicosen Oesophagusvene. *Munchen med. Wchnschr.* **42** 350, 1895.

33 Ogle, Cyril. Sarcoma of the Oesophagus. *Tr. Path. Soc. London* **47** 40 1896.

Donath von Licken, Frangenheim³⁴ Hotmann, Notthaft, Rieke³⁵ and Schmincke³⁶

Frattin³⁷ saw a lymphangio-endothelioma which constricted the entrance to the esophagus next to a bordering diverticulum Albrecht³⁸ described an alveolar sarcoma Carraro³⁹ saw a hemangio-endothelioma arising from the perithelium of capillaries

Frangenheim³⁴ found near the cardiac end of the stomach of a woman aged 63, a squamous carcinoma producing stenosis, above this however, was a polypoid polymorphocellular sarcoma The two tumors did not approach one another, being distinctly separated

Heixheimer⁴⁰ saw in an old man a carcinoma the stroma of which simulated completely the tissue of a spindle cell sarcoma The sarcoma had partly destroyed the carcinoma Sokolov⁴¹ considered this an adeno-sarcoma

Pratt⁴² and Lockyer⁴³ described a tumor which consisted partly of scirrhous carcinoma and partly of lymphosarcoma A metastasis to the liver in this case was found to be composed purely of lymphosarcoma tissue Socin⁴⁴ and Sommer also described carcinosarcoma of the esophagus

The tumors in the patients of Wolfensberger⁴⁵ and Glinski⁴ were considered by the authors as "rhabdomyoma" and as "mixed tumor with striated muscle," respectively These differentiate themselves from other sarcomas in that their course is relatively benign However Wolfensberger's case showed a metastasis to a gland behind the cardiac end of the stomach This was not a pure rhabdomyoma Aschoff also warned that a rhabdomyoma should be treated as a sarcoma Hacker stated that they metastasize frequently

34 Frangenheim, Paul Multiple Primartumoren, Virchows Arch f path Anat **184** 201 1906

35 Rieke Leber ein ausgedehntes medullar Sarkom des Oesophagus, Virchows Arch f path Anat **198** 526 1909

36 Schmincke Diskussionsbemerkung, Verhandl d deutsch path Gesellsch **17** 363 1914

37 Frattin Due casi di tumore primitivo in diverticuli del canale digerente, Polichimico (scz chir), 1903, vol 11

38 Albrecht Oesophagus Tumor, Wien klin Wchnschr **8** 332 1895

39 Carraro, N Sopra un caso di emangioendoteloma perivascolare primitivo dell'esofagus Pathologica **50** 611 1910

40 Heixheimer Gotthold Ueber das Karzinosarkom des Oesophagus Centrbl f allg Path u path Anat **29** 1 1918

41 Sokolov A Adenosarkom des Oesophagus Pathologica **4** 476 1912

42 Pratt quoted by Hacker and Lotharssen (footnote 9)

43 Lockyer quoted by Hacker and Lotharssen (footnote 9)

44 Socin Christoph Cor-Blt f Schweiz Aerzte **36** 953 1914

45 Wolfensberger Rudolf Ueber ein Rhabdomyom der Speiserohre Beitr path Anat u z allg Path **15** 460 1894

Metastases were not demonstrable in the rhabdomyosarcoma of the esophagus reported in this paper. Histologically, the tumor in my case was identical with that in the cases of the two authors mentioned except that myxomatous tissue was also found in the metastasis in Wolfensberger's case, also, cross-striations were demonstrated in both of the preceding cases. Wolfensberger showed drawings of the striations, but Glinski showed neither drawings nor photomicrographs of the tumor in his case. Wolfensberger interpreted the cellular elements of his tumor, other than the muscle present, as undifferentiated embryonal muscle cells and therefore called the tumor a rhabdomyoma. Glinski preferred to interpret the same cells as types differentiating into entirely different tissue, namely, giant cells, round cells, etc., and therefore called the growth in his case mixed tumor with striated muscle. He expressed the belief that these tumors arise from undifferentiated mesenchyme displaced when the marked developmental changes occur in the ventral floor of the embryonic foregut.

Rhabdomyomas occur most frequently in the urogenital system, in the uterus, vagina, bladder, testis and, particularly, in the kidney. A favorite site for the congenital lesion is in the heart. The tumor has been reported in isolated instances in the stomach, tongue, parotid gland, breast and prostate gland and in nearly all voluntary muscles of the body (Ewing²). Occurrence in the esophagus is most unusual, and has been reported in the literature only twice before. This case is the third on record.

PATHOLOGIC COMPLICATIONS AND METASTASES

Polypoid spindle cell sarcomas grow slowly and destroy little tissue. There may be no secondary pathologic lesions, as in the case reported.

The infiltrating and ulcerating round cell type can quickly reach a great dimension, tend to obstruct and close the lumen, compress the trachea and lead to edema of the larynx. Destruction due to severe necrosis and gangrene is not rare, nor is bleeding or ulceration with perforation into the trachea. There may be penetration to contiguous organs: purulent pleurisy, pulmonary gangrene and eventually esophageal perforation.

Metastases are most likely to occur in the diffuse infiltrating type of round cell sarcoma. They occur early and are widely distributed to lymph nodes, inner organs and bones. They appear more quickly than in carcinoma which according to most authors, metastasizes late. On the other hand, metastases are predominantly lacking in the circumscribed polypoid spindle cell sarcoma. Similarly, no metastases were found in the case reported. However, the spindle cell sarcoma in Donath's¹⁷ case did metastasize to the porta hepatis. Rhabdomyoma of

the large polypoid type as in Wolfensberger's⁴⁵ case, may also exhibit metastases to the lymph nodes

SYMPTOMATOLOGY AND DIAGNOSIS

Symptomatology—The clinical symptoms closely simulate those of carcinoma. Dysphagia occurs early, and may lead to complete closure and obstruction of the esophagus. Rieke is the only author who reported that dysphagia had not occurred in his case. In Albrecht's and Carrai's cases and in Donath's second case dysphagia must be assumed to have existed since the tumors were observed at autopsy, although nothing was reported regarding them. Sarcoma gives the appearance of slowly increasing stenosis. The sticking of food, its regurgitation and the vomiting of blood and pus are characteristic, but not constant, symptoms. Carcinoma as well as sarcoma can cause these symptoms. There is considerable pain. Its early appearance, piercing character and radiation between the shoulder blades is characteristic (Simon¹⁰). On the other hand, the course may be entirely symptomless and the lesion may be discovered only incidentally post mortem. The pain occurs frequently in attacks, frequently at night, and is not related to the eating of food. Deep-seated pain may simulate the symptoms of a pulmonary affliction or even an aneurysm (Hofmann¹⁸). In cancer of the esophagus, actual pain is conspicuous by its absence. The sense of discomfort present is due to the slight dilatation of the esophagus from the early narrowing of its lumen, together with colicky sensations of oppression due to increased muscular contractions of the organ (Abel¹). This can also be explained the symptoms of the patient in the case reported who never suffered very severe pain.

The stools may be black due to hemorrhage, as were those of my patient. The raising of pus may simulate pulmonary abscess.

Cachexia sets in early and earlier than in carcinoma. Von Eicken¹² attributed this to the pain, which destroys sleep at night and which leads to loss of appetite and to an emaciation greater than that which corresponds to the stenosis. This lack of correlation between the degree of stenosis and degree of emaciation allows one to suspect sarcoma.

Diagnosis—Sarcoma of the esophagus is clinically differentiated from carcinoma with difficulty (Simon¹⁰). The correct diagnosis has been made most often at necropsy (Hacker and Lotheissen⁹). Richard Cibo¹⁴ as a result of 3 000 postmortem examinations arrived at the conclusion that a greater proportion of mistakes in diagnosis had been made in cases of carcinoma of the esophagus than in any other condition. This might easily include sarcoma. Proper use of a sound may elicit

⁴⁶ Cibo Richard quoted by Abel (footnote 1)

valuable diagnostic information. Thus it can be inserted into the esophagus past a sarcoma more easily and with less injury and bleeding than past a carcinoma. This is true because of the latter's hardness and inflexibility, and because it usually involves the entire esophageal circumference, whereas sarcoma frequently involves only the anterior wall. By the resistance encountered, the level and the position of the tumor as well as the degree of stenosis may be determined. On withdrawal the sound may feel clasped more tightly at one certain point, the level of the lesion. In Gastpar's and Chapman's case no resistance was met with, in the latter because the lesion was high and partly in the pharynx.

Roentgenograms show the presence of stenosis, its level, its shape and its extent. It has been discovered that on ingestion of a contrasting material under fluoroscopy, the stream runs unimpeded down to the tumor, and here divides into two separate streams, which unite on reaching the stomach. This occurred with the slightest pathologic distortion of the esophageal wall by the tumor. Further observations must be made to determine whether such a roentgenographic observation, which is unusual for carcinoma, may be pathognomonic for sarcoma (Simon¹⁰).

Diagnosis can be certain only after esophagoscopy with biopsy and microscopic examination. Hacker said that his case in 1903 was the first on record in which the correct diagnosis of sarcoma of the esophagus was made during the life of the patient by biopsy section. Von Eicken saw a white necrotic membrane covering the lesion in his case. It bled easily when wiped with cotton. He thought that the condition was diphtheritic and administered antitoxin, with, of course, no result.

In making a diagnosis there must be considered, besides carcinoma, the benign tumors found on rare occasions. The following have been reported: pedicled polyps, multiple papillomas, fibromas, lipomas, myxomas, angiomas, warts and various cystic formations, also, adenomas and myomas, both of the smooth and of the striated type, also, tuberculomas and gummas.

Von Eicken¹² considered the slow growing spindle cell sarcomas operable lesions, the fast growing round cell types, inoperable, hence, the importance of exact microscopic diagnosis.

TREATMENT AND PROGNOSIS

Treatment—The operative treatment for sarcoma in the thoracic esophagus offers little prospect of success. No successful case was found reported. Recurrence and metastases are more frequent than in carcinoma. Nevertheless, attempt at resection is justified. Such a procedure has been successful for carcinoma as in Torek's⁴⁷ famous

⁴⁷ Torek, I. The Causes of Failure in the Operative Treatment of Carcinoma of the Oesophagus. *Ann Surg* 90:496, 1920.

case His patient lived thuteen years after the operation and died of intercurrent disease Eggers's⁴⁸ first patient with carcinoma was living at the end of one year and his second patient was living with metastases at the end of a similar period Lotheissen's⁴⁹ patient died from cardiac syphilis five months after surgical extirpation The patients in Hedblom's⁵⁰ and Zaaier's⁵¹ successful cases lived only a few months after the operation (Torek⁴⁷) Successful cases have also been reported by Bircher Kummell Kuttner, Volcker and Brun (Torek⁴⁷) Operative cure of carcinoma of the cervical esophagus has been repeatedly accomplished (Torek) On the other hand, sarcomas located high in the esophagus have also been resected successfully Hacker⁸ was the first to do this in 1909 in a case of tumor of the anterior wall of the cervical esophagus The microscopic nature of the tumor was later confirmed He first did a gastrostomy, and five weeks later resected the esophagus Six weeks later, there was recurrence of the tumor Three months after the operation and before the wound had completely healed, the patient died from weakness and aspiration pneumonia Snoy⁵² had a patient, aged 57, with a sarcoma involving the larynx and entrance to the esophagus He did a tracheotomy and gastrostomy first, later he successfully performed the radical extirpation After several months no recurrence of the tumor followed and only an impairment of speech and distortion of the larynx and tongue remained

Exploratory operations in sarcomas of the esophagus have been done supposedly for other conditions Thus one author thought his patient had a subphrenic perigastric abscess Donath saw metastatic tumors in the abdomen which he thought arose from the stomach

In the literature there is a record of gastrostomy having been done three times because the patient was insufficiently nourished Frattin's patient lived some time after such an operation, von Eicken's died soon from weakness and Ogle's patient developed peritonitis My patient lived four months Von Eicken recommended gastrostomy for all patients with dysphagia Regurgitation of injected nutrients may, however be a serious complication

48 Eggers C Carcinoma of the Thoracic Portion of the Oesophagus, Surg Gynec Obst **50** 630 1930

49 Lotheissen, G Die Resektion der Speiserohre Wien med Wchnschr **79** 618 1929

50 Hedblom C A Combined Transpleural and Transperitoneal Resection of Thoracic Esophagus Surg Gynec Obst **35** 284 1922

51 Zaaier J H Erfolgreiche transpleurale Resektion eines Kardiakarzinoms Beitr z klin Chir **83** 419, 1913

52 Snoy Sarkom der Pharynx-Oesophagusgrenze mit Erfolg operiert nach vorhergehender Gastrostomie Med Klin **7** 58 1911

Perhaps more permanent cures may be effected by postoperative irradiation in sarcoma. Radium should be employed for palliation in inoperable cases to halt the destruction, probably even to make swallowing possible again and to mitigate the pain. This can be combined with the use of the galvanocautery. Spindle cell sarcomas are resistant to radium, 1,050 millicurie hours appeared insufficient in the case reported, as shown at necropsy. The dose could easily have been doubled had not perforation been feared. The effect of deep roentgen therapy on the tumor in this patient, over the previously treated thyroid area, appeared definite. Rapid proliferation was deferred, perhaps from one and a half to two years.

Prognosis—Because of the usual extremely rapid course of the disease, the prognosis is graver than in carcinoma. Death is due to exhaustion, frequently starvation, as in the cases of Paget,⁵³ Chapman,⁶ Targett,²⁶ Stephan,¹¹ Gastpar,¹⁵ Ghnski,⁴ Wolfensberger,⁴⁵ Eppinger,²⁸ and Hacker's first case. It also occurs from perforation into adjacent organs producing mediastinitis, etc. The lesion may perforate into the trachea (Shaw,²⁵ Wegener²¹ and Baur¹⁶) and lead to destruction of lung tissues with abscess formation and gangrene (Rolleston,²⁰ Baur,¹⁶ Livingood,³¹ and Starck's⁷ second case) or to intercurrent disease like pneumonia (Albrecht,³⁸ Rieke,³⁵ and Donath's¹³ second case). Notthaft's³² patient died of hemorrhage from esophageal varices caused by cirrhosis of the liver. Generalized metastases may be another cause of death. My patient died of suffocation. The duration of life is only about five or six months when dysphagia has developed.

SUMMARY AND CONCLUSIONS

Sarcoma of the esophagus is rare. Less than fifty cases have been reported in the literature, only about thirty unquestioned cases have been reported (Simon,¹⁰ 1928). Though a disease of persons of advanced years, it occurs more frequently in the young than does carcinoma. It occurs most frequently in the lower third of the esophagus, carcinoma appears in the middle third. There are two chief types of sarcoma: the polypoid, which contains spindle cells, is relatively benign and very rarely metastasizes, and the diffuse infiltrating type, which contains round cells and early gives rise to distant metastases.

The tumor in the case herewith reported was a polypoid rhabdomyosarcoma and contained muscle cells of the striated type, spindle cells, giant cells, round cells and fibrous connective tissue. Unlike carcinoma, pain in sarcoma is often early and severe. Marked emaciation may develop long before appreciable stenosis. Dysphagia is often not the

⁵³ Paget, Stephen. Unusual Form of Malignant Disease of the Oesophagus. Tr. Path. Soc. London 46: 46, 1895.

earliest symptom, but rather vague sensations of pressure and constriction. The condition is usually wrongly diagnosed. Most of the reported cases were correctly diagnosed only at necropsy. Diagnosis is certain only after biopsy and microscopic examination. Exact microscopic diagnosis is a valuable aid in determining operability. Sarcoma of the cervical esophagus has been resected successfully, sarcoma of the thoracic esophagus never has. The tumor in my case was refractive to 1,050 millicurie hours of radium. Deep roentgen therapy appeared to arrest the process for from one and a half to two years.

My case was unusual among the reported cases, because it was a rhabdomyosarcoma and because it occurred in the cervical region of the esophagus, in a woman and at a relatively early age. Among lesions of its type it was extraordinarily favorable to operation had it been possible to make the correct diagnosis early.

GALLBLADDER FUNCTION

I THE CONTRACTILE FUNCTION OF THE GALLBLADDER

I S RAVDIN, MD

AND

J L MORRISON, BS

PHILADELPHIA

Nearly a decade has passed since interest in the controversy over the emptying of the gallbladder was reawakened. During this time much has been said on both sides of the question. Any one familiar with current literature is aware that at present opinion is so divided that it seems impossible to reconcile the various views. Opinion is divided not only among clinicians, but among those who have carried out experimental work, as Levine¹ has pointed out. In fact, the major controversy at present exists in the group that has studied the mechanism of the gallbladder in the experimental laboratory.

On one side one finds Sweet,² Halpert,³ Demel and Brummelkamp,⁴ and Blond,⁵ who are the chief advocates of the theory that the gallbladder does not empty through the cystic duct, on the other side, Elman and McMaster,⁶ Whittaker,⁷ Higgins and Mann,⁸ Ivy and Oldberg,⁹ and Boyden,¹⁰ who believe that the gallbladder contracts to expel bile through the cystic duct.

There are also those who believe that the gallbladder is emptied through the cystic duct, but that this is accomplished by forces other than the contractile force of the musculature of the gallbladder. Winkelstein and Aschner¹¹ stated that respiratory movements influence emptying of the gallbladder by affecting intraperitoneal pressure.

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1 Levine, S. Contractions of the Gallbladder as Seen in Man, *Arch Int Med* **40** 420 (Oct) 1927

2 Sweet, J. E. *Internat Clin* **34** 187, 1924, *Ann Surg* **90** 939 1929

3 Halpert, B. *Med Klin* **20** 408 1924, *Am J Physiol* **88** 351, 1929

4 Demel, R., and Brummelkamp, R. *Mitt a. d. Grenzgeb. d. Med. u. Chir.* **37** 515 1924

5 Blond, K. *Arch f. klin. Chir.* **149** 662, 1928

6 Elman, R., and McMaster, P. D. *J. Exper. Med.* **44** 151, 1926

7 Whittaker, L. R. *Am J Physiol* **78** 411, 1926

8 Higgins, G. M., and Mann, F. C. *Am J Physiol* **78** 339 1926

9 Ivy, A. C., and Oldberg, E. *Am J Physiol* **86** 599, 1928

10 Boyden, E. A. *Anat. Rec.* **40** 147 1925, *Surg. Gynec. Obst.* **46** 30 1928

11 Winkelstein, A., and Aschner, P. W. *Am J. M. Sc.* **171** 104 1926

Graham¹² expressed the belief that the flow of bile from the liver through the common duct exerts a siphonage action on the gallbladder, while Burget¹³ and Copher and Kodama¹⁴ stated that duodenal peristalsis is the major factor which affects the flow of bile from the gallbladder.

Every one agrees on one fact, which is that, by one mechanism or another, the gallbladder is emptied of its contents, whether this is through the lymphatics, the blood vessels or the cystic duct. Workers in this laboratory had come to believe that those in favor of noncontractile function had the stronger side of the argument until about four years ago, when certain observations induced us to investigate the subject further. Data accumulated since that time have led us to believe that both processes, absorption and contraction, play a part in the emptying of the gallbladder.

MUSCULATURE

It is not to be denied that the musculature of the gallbladder is not as thick as that of the stomach, intestine or urinary bladder, but that muscle tissue is present is obvious from even cursory microscopic study of sections of the organ. The denial of sufficient muscle for function seems to be based on the fact that if nature expected bile to be forced out of the gallbladder through the cystic duct, it would have endowed this structure with a more abundant supply of muscle tissue. The answer could be easily made that if as much muscle tissue as is present is not to be used for contraction it is a unique anatomic condition.

Muscle tissue is present, it is more abundant in some species than in others. It varies in amount, but we have not examined the gallbladder of any species which does not have some muscle tissue (fig. 1).

LYMPHATICS AND BLOOD VESSELS

Sweet,¹⁵ Halpert,³ and Demel and Brummelkamp⁴ are exponents of the theory that the bile which enters the cystic duct leaves the gallbladder by way of the lymphatics. That absorption of certain substances—particularly water and sodium chloride, probably bile salts and perhaps cholesterol—takes place is generally believed. Whether this absorption takes place chiefly by the lymphatics or by the blood vessels is yet to be determined. That other constituents of the bile, especially pigment proteins and mucus pass out in considerable amounts through similar pathways seems to us to be open to considerable question.

12 Graham E. *Am J M Sc* **172** 625 1926, *Surg Gynec Obst* **44** 153 1927. Graham, E. Copher G. H. and Kodama S. *J Exper Med* **44** 65, 1926.

13 Burget G. E. *Am J Physiol* **74** 583, 1925.

14 Copher G. H. and Kodama S. *Regulations of Flow of Bile and Pancreatic Juice into Duodenum* *Arch Int Med* **38** 647 (Nov.) 1926.

Our renewed interest in this problem arose from the fact that we have never been able to demonstrate bile pigment in the lymph from the gallbladder. Theoretically, we would expect to find it if the gallbladder bile passed in toto from the gallbladder by absorption instead of by the cystic duct.

The lymph drainage from the unobstructed gallbladder of the cat or dog did not in any instance, in many experiments, show the presence of bile pigment in amounts sufficient to demonstrate it by any method known to the physiologic chemist. It seemed possible that bile pigment



Fig 1—Muscularis and submucosa of the gallbladder of the dog

might gain access to the venous return from the gallbladder, but investigations to determine this were entirely negative. We have never found enough pigment in blood taken from the cystic vein to make qualitative estimations, this is also true of the blood of the peripheral vein of the normal dog. We have introduced solutions of bilirubin into the gallbladder, with the hepatic ducts ligated, and have likewise been unable to demonstrate the disappearance of bile pigment through the lymphatics or veins. Quantitatively we were able to recover what was introduced within experimental limits.

Dyes introduced into the gallbladder of dogs and guinea-pigs in which the common duct was intubated so as to recover any dye that escaped through the cystic duct left the gallbladder slowly through the lymph or blood vessels of the wall of the gallbladder. These dyes escaped rapidly through the cystic duct when contraction of the gallbladder was stimulated. Winkenwerder¹⁵ has recently shown that many of the absorption studies previously done bear close scrutiny because of failure to control the experiment properly. He has, however, concluded, after a careful study, that the epithelium of the extra-hepatic system, with the exception of that of the smallest bile ducts, is permeable to certain crystalloids.

We placed bile and solutions of bilirubin in an excised gallbladder, which we immersed in a Ringer-Locke solution which was kept at 38 C. We were interested in ascertaining the rapidity with which pigment would dialyze through the wall of the gallbladder. Repeated study of the Ringer-Locke solution over a three hour period failed to show that the pigment was passing through the gallbladder into the surrounding fluid.

From our studies we were led to conclude that certain constituents of bile must leave the gallbladder by channels other than those provided by the lymphatics or blood vessels—a view which has been strengthened as our work has continued.

OBSERVATIONS IN MAN

Pendergrass, Overholt and one of us (I S R) were extremely fortunate last summer in observing what we believed to be rhythmic tonic contractions in a human gallbladder. The patient had previously had cholecystostomy and common duct drainage for a lesion in the head of the pancreas. During her convalescence we introduced iodized rape seed oil into the gallbladder and observed the organ fluoroscopically. The patient was asked to stop breathing for short periods, during which we clearly saw alterations in the size and shape of the organ, which we interpreted to be the result of contraction of the gallbladder.

Pendergrass has recently obtained roentgen evidence that sodium tetraiodophenolphthalein can leave the gallbladder by way of the cystic duct. After the dye was visualized in the gallbladder and sufficient time had elapsed for its concentration in the gallbladder as evidenced by intensification of the shadow a meal of fat was given and the patient was examined under the fluoroscope every few minutes. Within a short time the cystic duct was visualized and then the common duct (figs. 2, 3 and 4). Ivy and Oldberg¹⁶ have obtained similar roentgenograms after the injection of cholecystokinin in animals.

¹⁵ Winkenwerder, W. L. Bull. Johns Hopkins Hosp. 46:296, 1930.



Fig 2—Human gallbladder, partial concentration



Fig 3—The gallbladder immediately preceding meal or fat

It can be said that in these experiments we did not actually see the gallbladder contract. Actual observation in the intact animal is not possible and a normal physiologic response in the anesthetized animal or human being whose abdomen is open cannot be expected. We, therefore, have studied the response of the completely isolated gallbladder to drugs, assuming that if the species that we studied responded to drugs as other smooth muscle with a similar innervation responded, we should have additional evidence that the musculature did not exist without functioning.



Fig. 4—The gallbladder immediately after meal of rat

THE RESPONSE OF THE ISOLATED GALLBLADDER TO DRUGS

In these studies we used the gallbladder of the dog, guinea-pig and *Macaca mulatta* monkey. The gallbladder was excised, the bile removed and the gallbladder placed in a Ringer-Locke solution that had been well oxygenated. The temperature of the solution was maintained at 38.5°C by a Harvey thermoregulator equipped with a telegraphic relay. The entire gallbladder was used. The fundus was attached in the lower end of the bath and the neck to a lever devised by Muschat.¹⁶ The cystic duct was excised in all experiments.

¹⁶ Muschat, M. J. *Pharmacol. & Exper. Therap.* **37**: 297, 1929.

Several interesting observations were made. The contraction in response to stimulation of the guinea-pig's gallbladder was observed as long as twenty-five hours after its removal from the animal, and tonus waves for a longer time. In some instances, the gallbladder was attached so as to demonstrate circular contraction after it had been arranged for demonstration of longitudinal contractions. No difficulty was encountered in demonstrating these, two types of contractions could be obtained constantly.

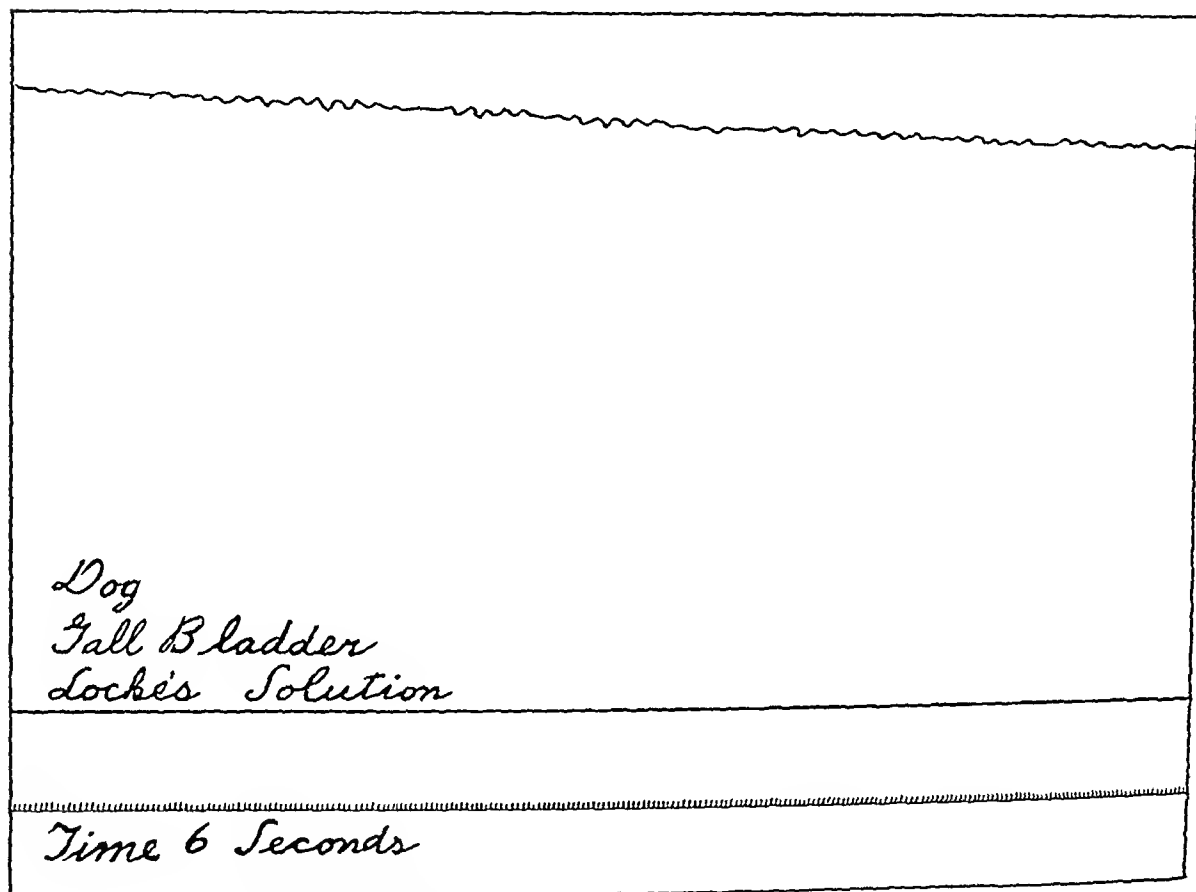


Fig 5—Rhythmic contractions, isolated gallbladder of the dog

Rhythmic Contractions—Rhythmic contractions were demonstrated in the dog guinea-pig and rhesus monkey (figs 5, 6 and 7). The rate varied somewhat, even in the same species, but usually from three to six tonus waves per minute were observed. The strength of the tonus waves varied. They were, as a rule, more forceful from fifteen to twenty minutes after immersion in the bath than they were at the beginning. The temperature of the bath affects the tonus of the gallbladder. Tonus increases up to 41 C and then decreases. Rhythmic contractions that were not visible at 36 C became visible between 37 and 38 C (fig 8).

Survival of Muscular Activity—Tonus waves of the gallbladder of the guinea-pig were demonstrated for as long as twenty-seven hours after isolation of the gallbladder. In the dog and monkey no attempt was made to determine the total length of time over which an individual preparation would respond, but tonus waves were observed in

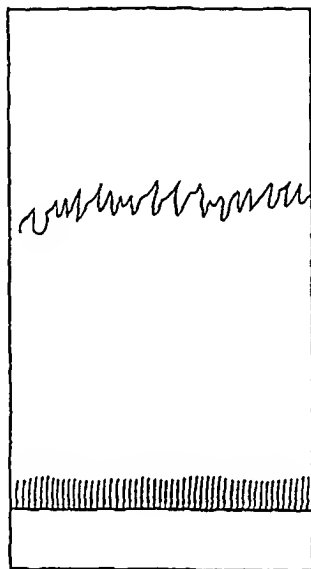


Fig 6—Rhythmic contractions, isolated gallbladder of the guinea-pig

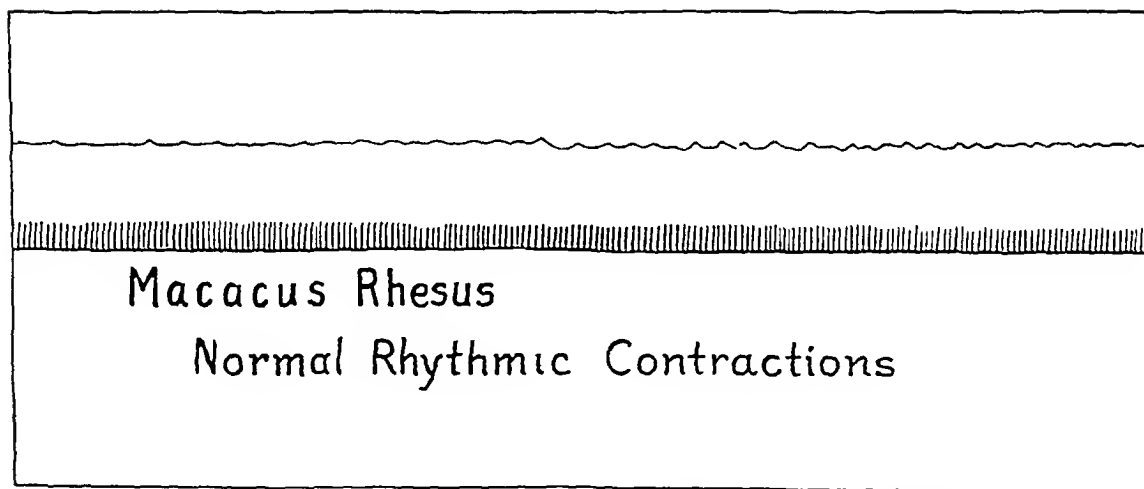


Fig 7—Rhythmic contractions, isolated gallbladder of the monkey

preparations for a period of several hours. In the dog, especially, it was necessary to have from ten to fifteen minutes elapse between maximum contractions after stimulation if similar responses were to be expected. Contractions of maximal character were obtained with the guinea-pig's gallbladder after stimulation twenty hours after immersion in the Ringer-Locke solution (fig 9).

Pilocarpine—This drug consistently caused stimulation of the isolated guinea-pig's gallbladder (figs 10 and 11) Muscular activity following the administration of pilocarpine was paralyzed by the addi-

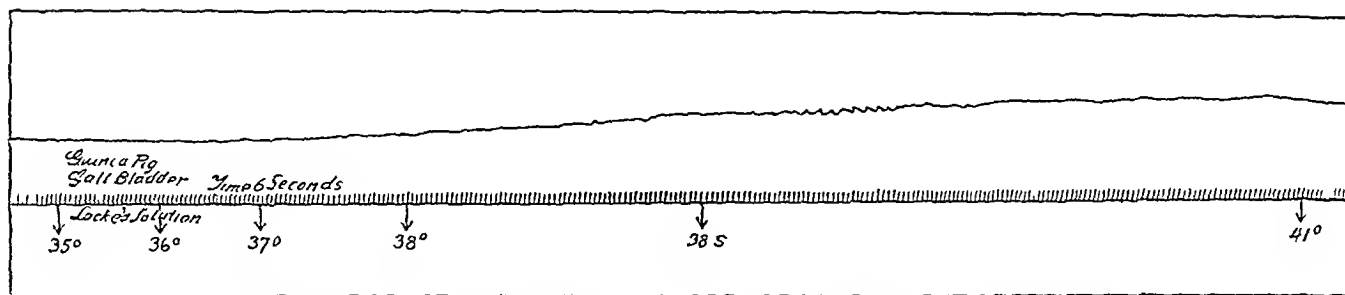


Fig 8—Effect of temperature on the isolated gallbladder of the guinea-pig

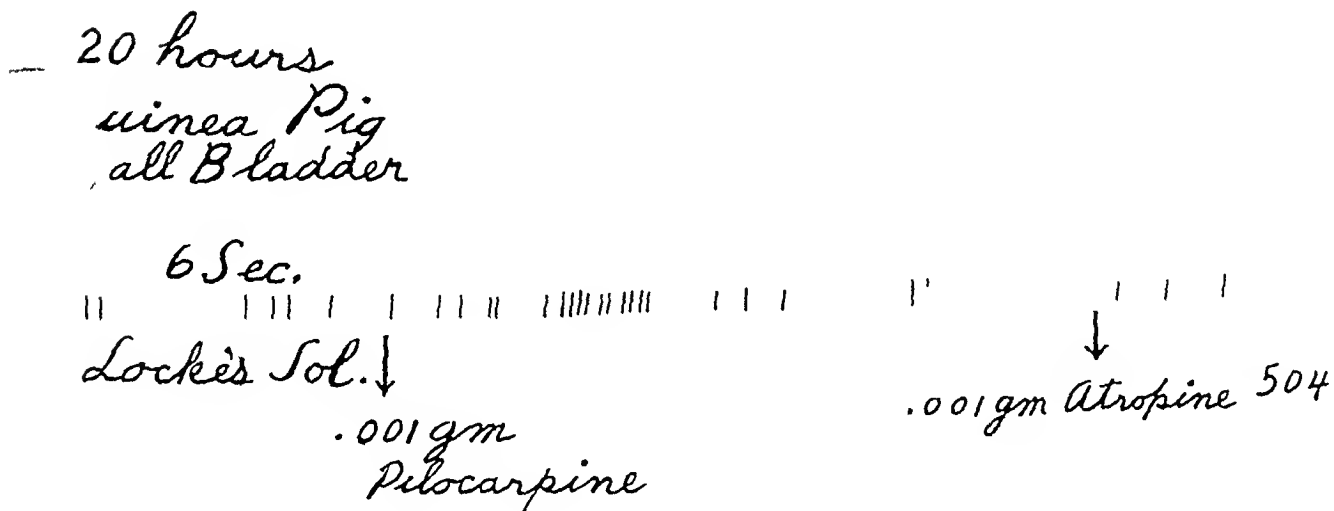


Fig 9—Response to pilocarpine stimulation of the guinea-pig's gallbladder twenty-four hours after isolation

tion of atropine sulphate. The gallbladder responded actively after pilocarpine, but if it was stimulated immediately with the same drug before rhythmic contractions had returned, the contraction was of a much slower and less forceful type. Figure 12 demonstrates the

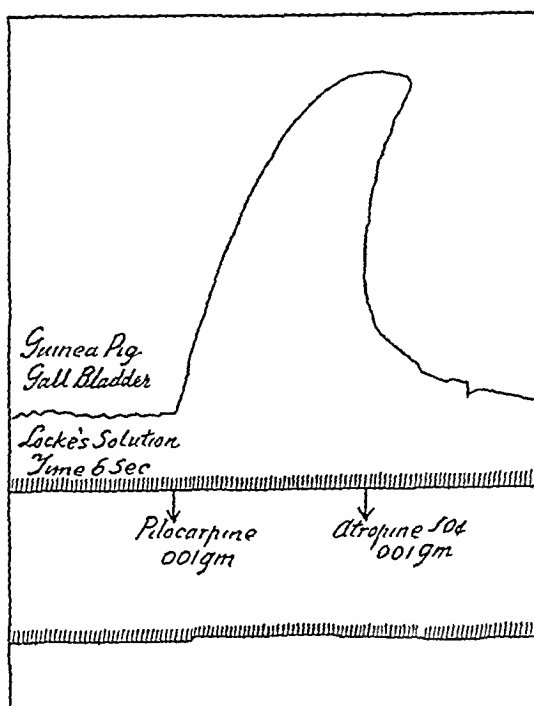


Fig 10 —Response of the isolated gallbladder of the guinea-pig to pilocarpine

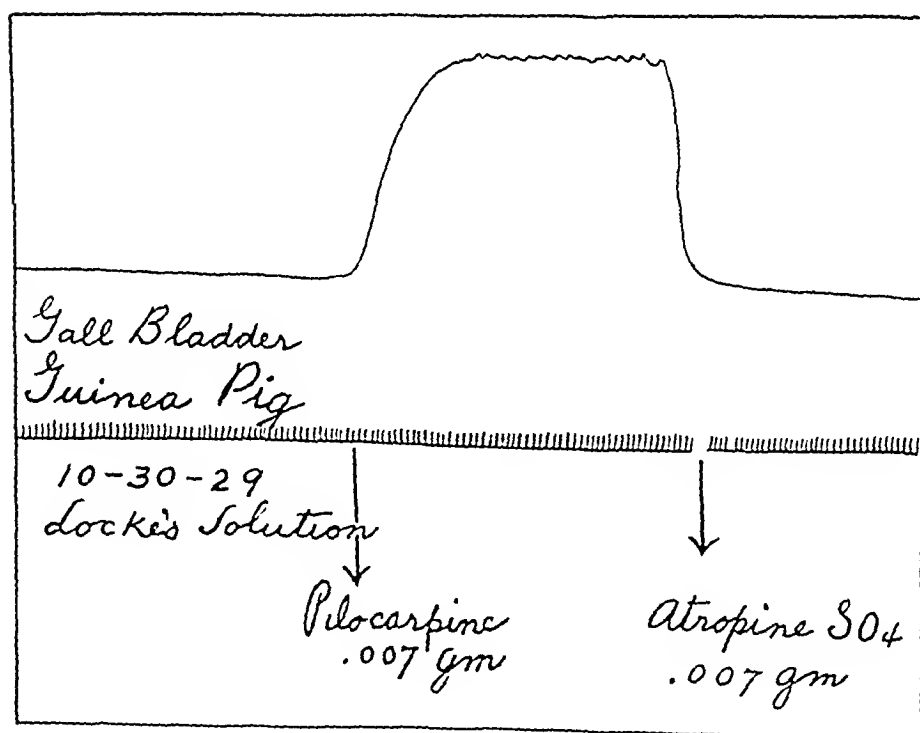


Fig 11 —Response to pilocarpine stimulation of the isolated gallbladder of the guinea pig

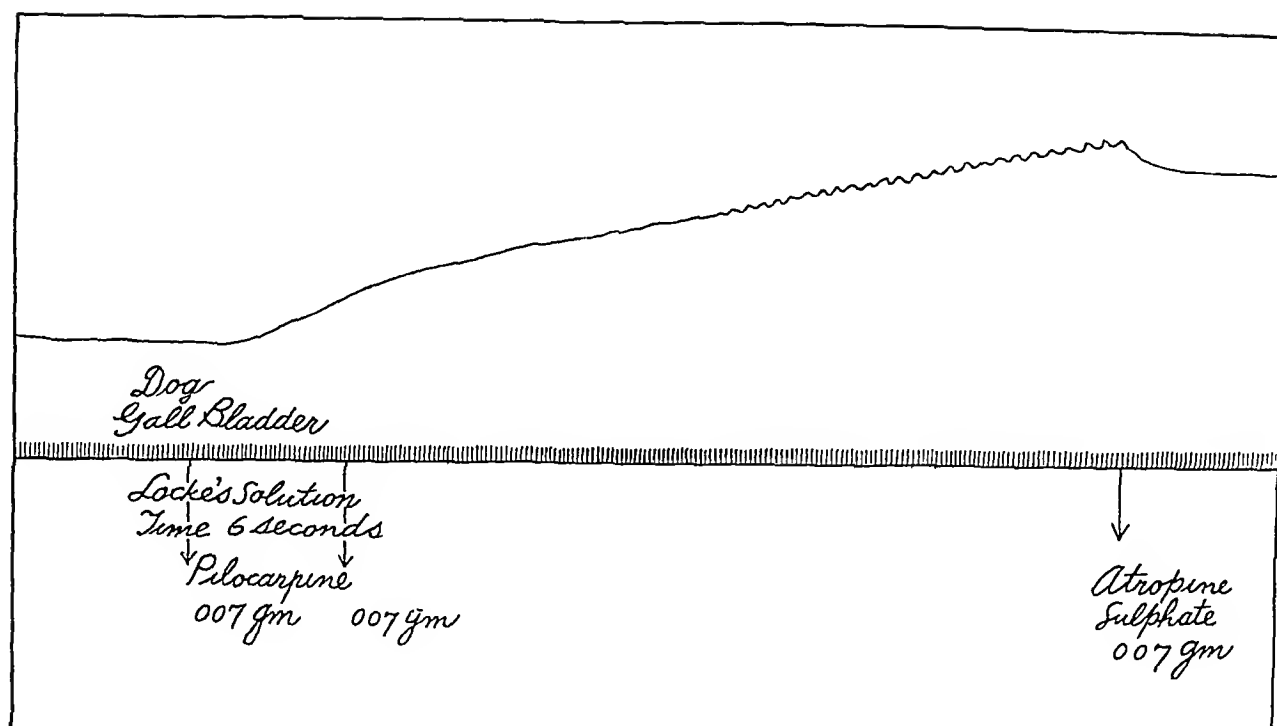


Fig 12—Response of the isolated gallbladder of the dog to pilocarpine stimulation

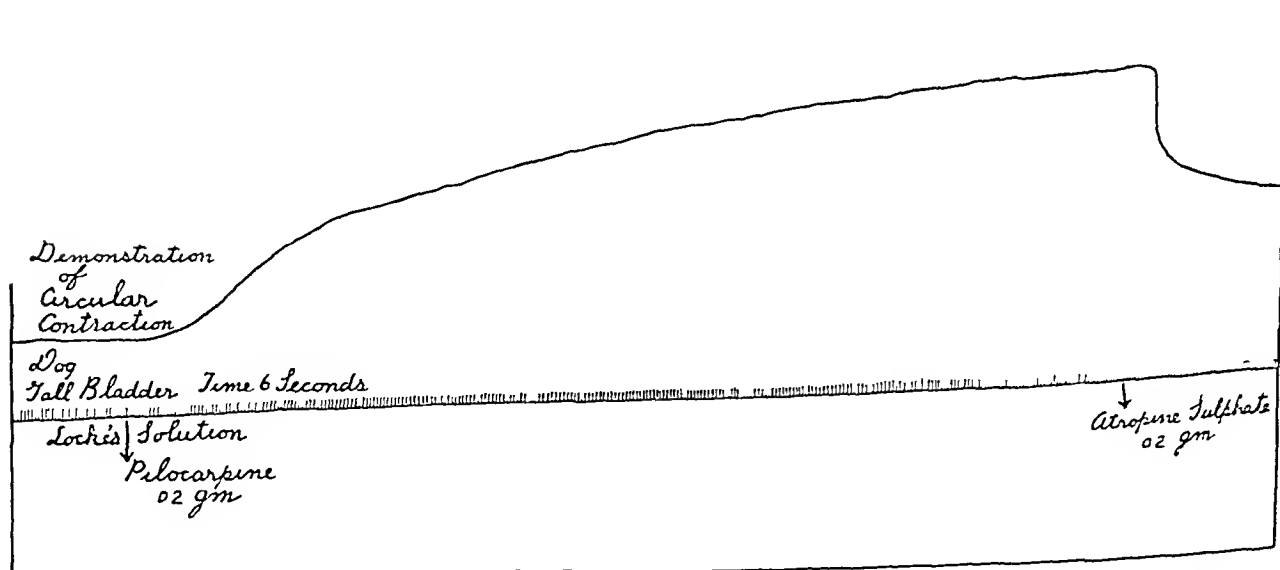


Fig 13—Circular contraction under pilocarpine stimulation of the isolated gall bladder of the dog

response in the isolated gallbladder of the dog. Figure 13 illustrates the response obtained from the gallbladder when arranged to demonstrate circular contraction. Figure 14 is the tracing obtained from the gallbladder of *Macacus rhesus* after stimulation with pilocarpine.

Histamine Diphosphate—This drug caused a response similar to that obtained with pilocarpine. It caused vigorous contraction of the isolated gallbladder with an increase in the size of the tonus waves after the solution in the bath had been changed. The response to this drug was similar to that obtained after stimulation of a smooth muscle preparation from the cornu of the virgin guinea-pig's uterus with histamine. Figure 15 is an illustration of the response of the guinea-pig's

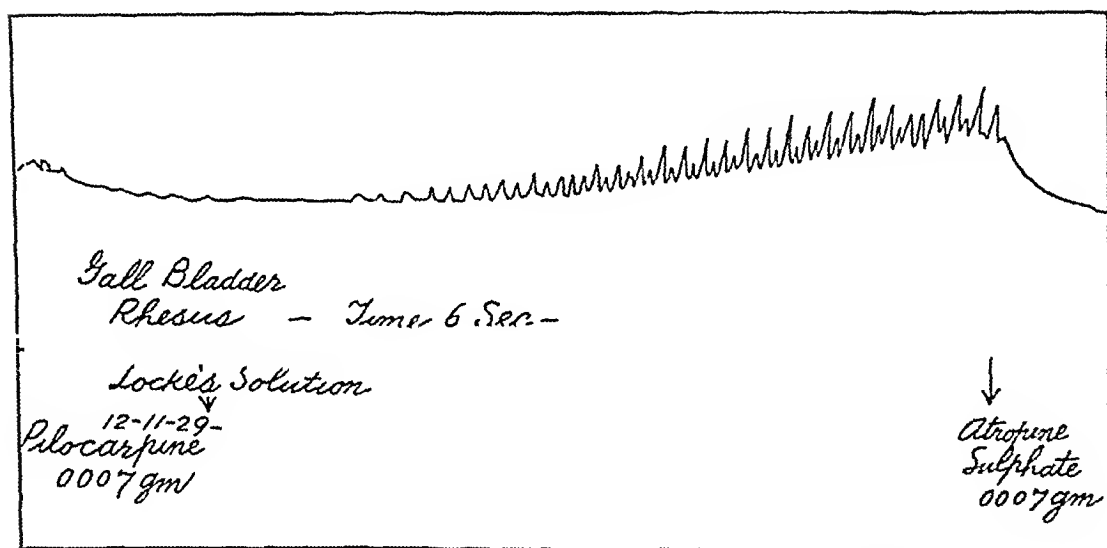


Fig 14—Response to pilocarpine stimulation of the isolated gallbladder of the monkey

gallbladder to histamine twenty-four hours after isolation, while figure 16 shows the response of *Macacus rhesus* to the same drug. The dosages recorded are in terms of the salt and not in terms of histamine base.

Secretin—Although numerous investigators have believed that the gallbladder contracts in response to a hormone, it remained for Ivy and his co-workers to bring forth strong evidence (cholecystokinin) in favor of this view. Figure 17 shows the response obtained from a guinea-pig's gallbladder with a preparation of secretin made from duodenal mucous membrane after the method of Mellanby. It shows a slow increase in tonus over a period of minutes, the time marker indicating six-second periods.

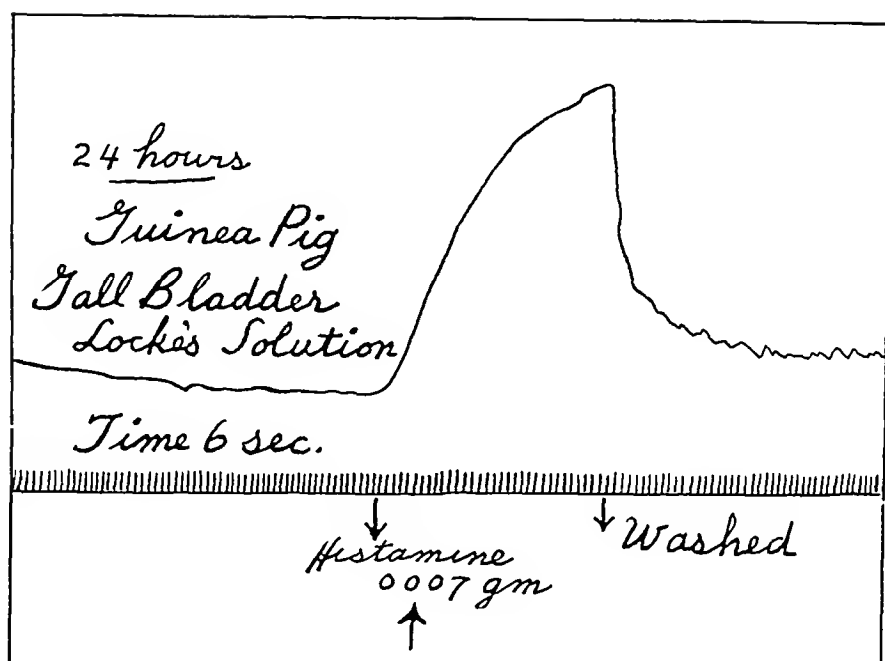


Fig 15—Response of the isolated gallbladder of the guinea-pig to histamine
The gallbladder had been isolated twenty-four hours previously

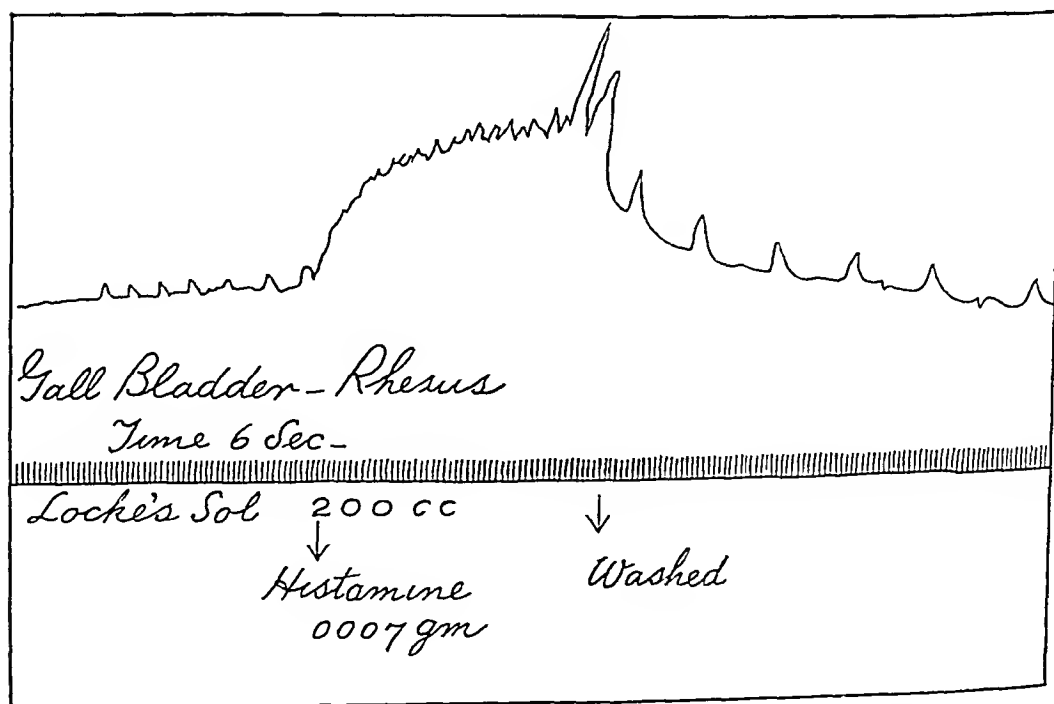


Fig 16—Response of the isolated gallbladder of the monkey to histamine

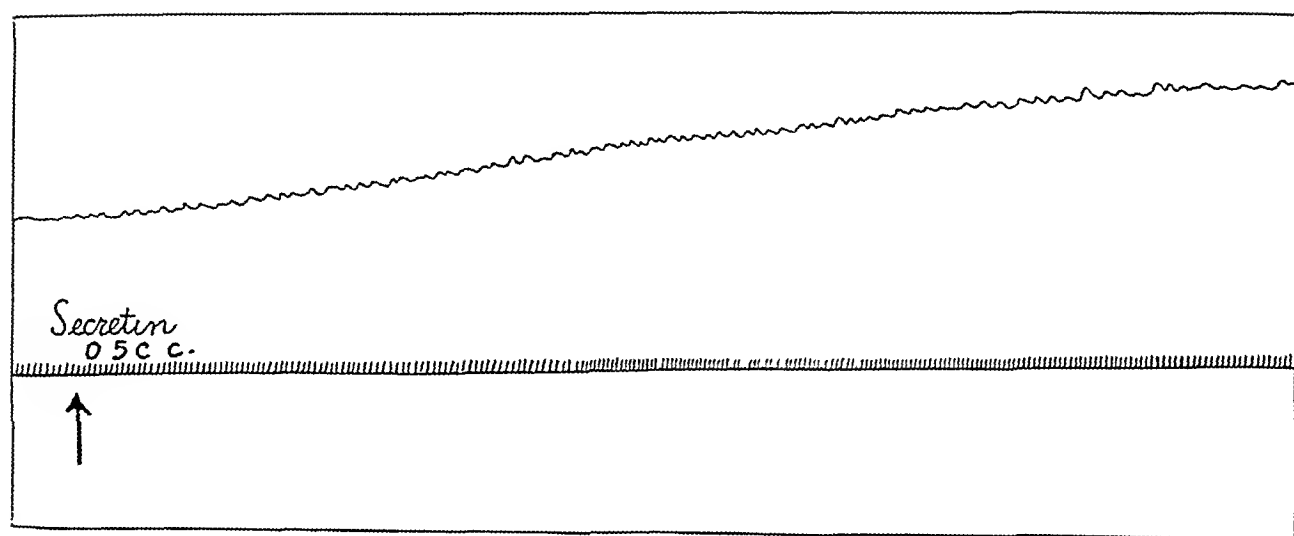


Fig 17—Response of the isolated gallbladder of the guinea-pig to secretin

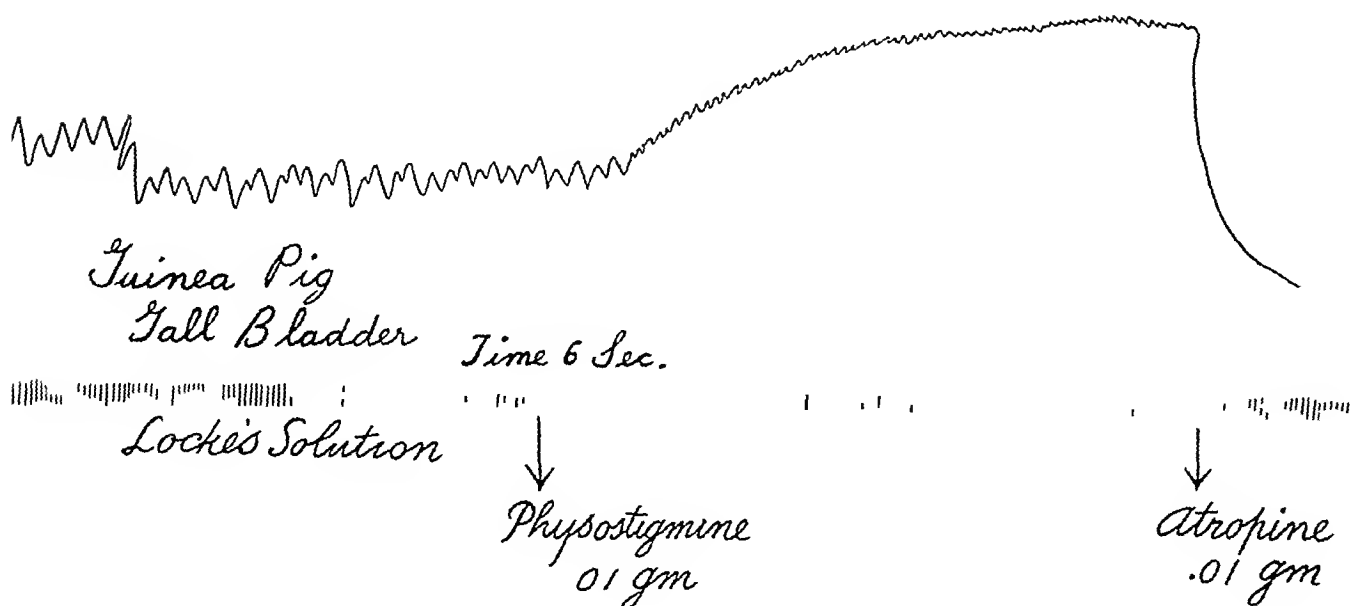


Fig 18—Response of the isolated gallbladder of the guinea-pig to physostigmine

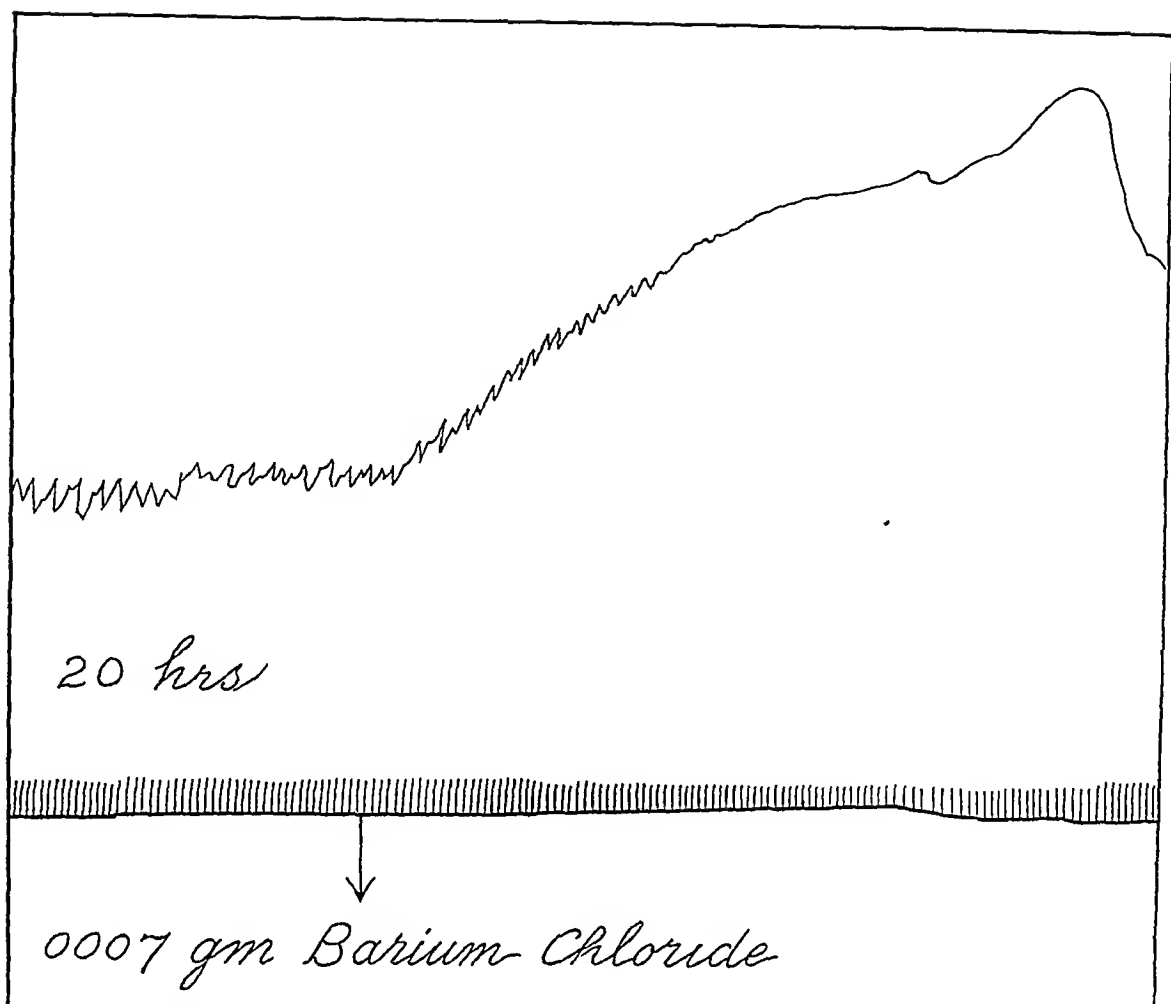


Fig 19—Response of the isolated gallbladder of the guinea-pig to barium chloride

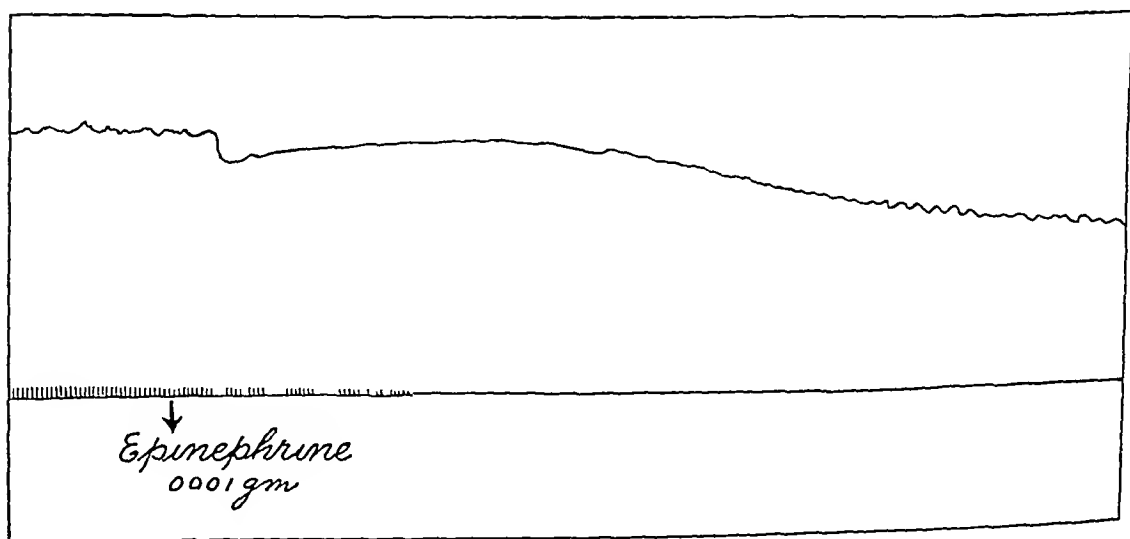


Fig 20—Effect of epinephrine on the tonus of the isolated gallbladder of the guinea pig

Other Drugs—Physostigmine also caused contraction of the gallbladder musculature (fig 18), as did barium chloride (fig 19). The muscle was paralyzed after the addition of atropine. Contrary to the

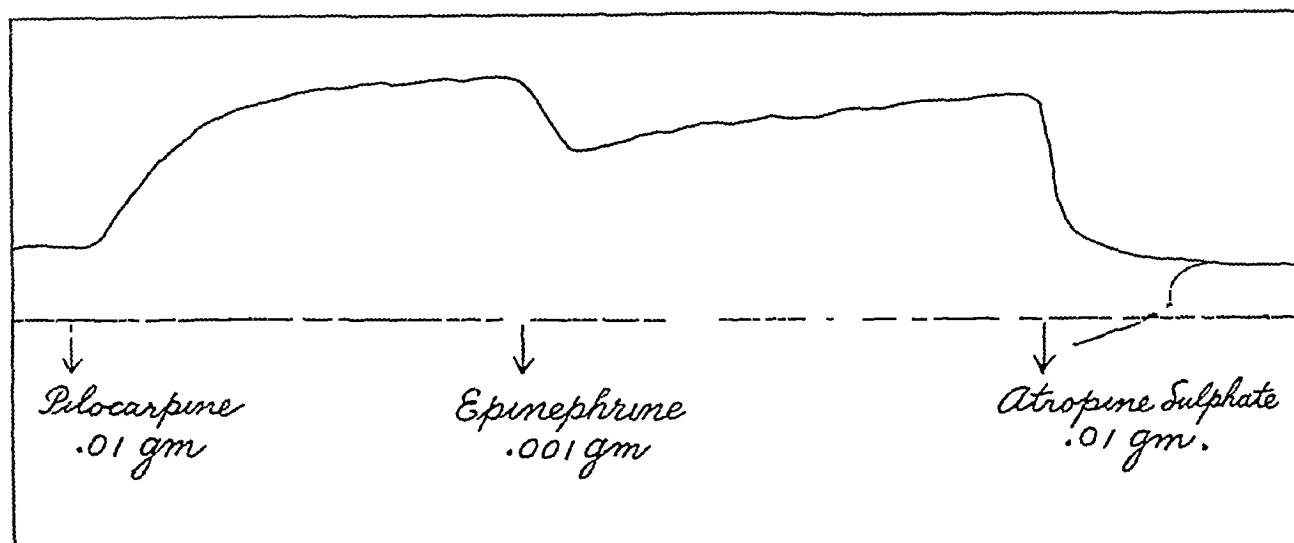


Fig 21—The effect of epinephrine on the tonus of the isolated gallbladder of the guinea-pig

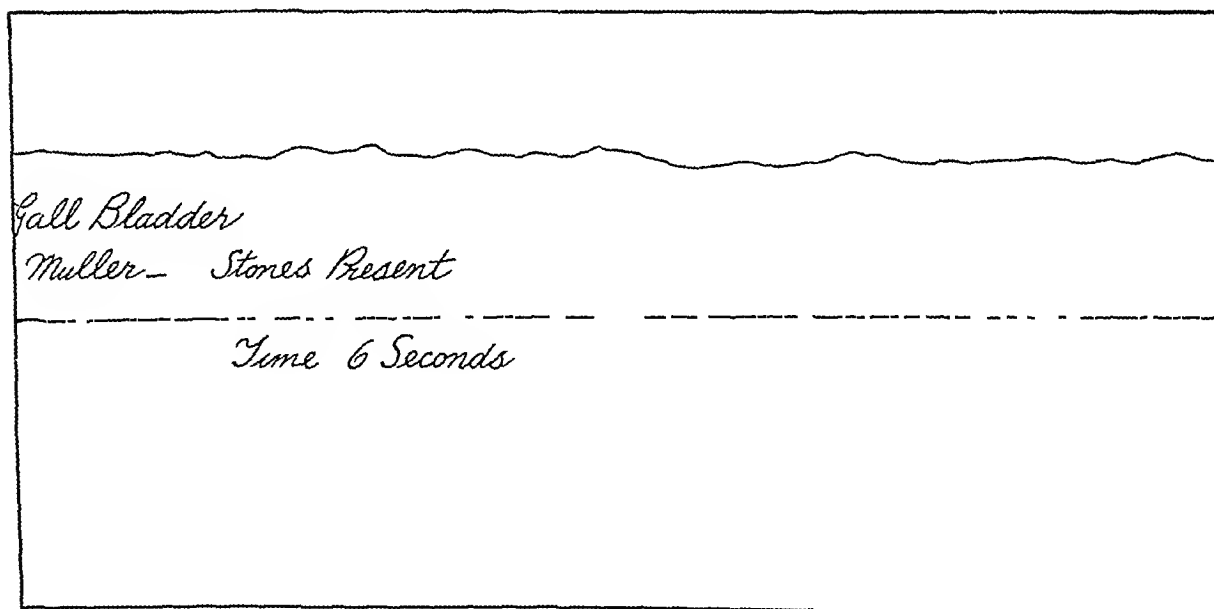


Fig 22—Contractions obtained from a diseased human gallbladder without stimulation

observations of some investigators, we have found that epinephrine causes relaxation of the gallbladder (figs 20 and 21). In only one experiment of the many that were performed did we observe contraction of the gallbladder following its use.

The Human Gallbladder —We have not been fortunate enough to obtain a normal human gallbladder for study. That such a gallbladder would respond as do those of the animals we have studied, we cannot question. That even the diseased human gallbladder will show abortive spontaneous contractions is illustrated in figure 22. This gallbladder contained calculi and was the site of chronic interstitial inflammation.

COMMENT

We do not intend to discuss the entire literature on the subject of gallbladder function, which is indeed voluminous, and which was so admirably reviewed by Mann¹⁷ in 1924. Statements are conflicting, and numerous observers have merely repeated older experiments with which they apparently were not familiar. We wish merely to point out a few of the contributions that would tend to confirm the view that we hold that among other functions, some of which may not as yet be known, the gallbladder possesses the ability to contract. With proof of this, it remains for the future to prove whether this mechanism is or is not present for a definite physiologic purpose. The burden of proof rests on those who deny its contractile function.

Freeze,¹⁸ in a paper that seems to have been overlooked by many, found that the gallbladder when stimulated through its motor nerves is capable of contracting against a pressure of at least 220 mm of Ringer's solution. We obtained figures higher than this for a dog when the cystic duct was connected to a water manometer after the injection of pilocarpine. Our experiment was subject to the error that contiguous structures and vascular effects might have caused a part of the response. Contractions of the magnitude reported by Freeze, while weak when compared to the response obtained from the urinary bladder, nevertheless show a magnitude sufficient to cause bile to leave the gallbladder by way of the cystic duct.

Bainbridge and Dale,¹⁹ in an excellent article published shortly after Freeze published his work, confirmed Doyon's observations of spontaneous rhythmic contractions in the gallbladder. They confirmed the suggestion of Langley, and our data further confirm this, that epinephrine caused relaxation of the gallbladder. They do not agree with Freeze on the exact course of the major motor and inhibitory fibers, but do agree that both sets of fibers are supplied to the gallbladder. Whittaker⁷ has obtained contraction of the gallbladder when the nerve supply has been severed. This does not invalidate the previous observations, but demonstrates that the gallbladder can contract inde-

17 Mann, F. C. *Physiol. Rev.* **4**: 251, 1924.

18 Freeze, J. A. *Bull. Johns Hopkins Hosp.* **16**: 235, 1905.

19 Bainbridge, F. A., and Dale, H. H. *J. Physiol.* **23**: 138, 1905.

pendent of its connection with the central nervous system. Bainbridge and Dale believed the increase in tone of the gallbladder in response to pilocarpine to be due to swelling of the liver. This we have shown is not the case, since the isolated gallbladder responds similarly.

In 1915, Lieb and McWhorter²⁰ studied the action of drugs on strips of the gallbladder by a method similar to that which we have used, and in 1925, Ischiyama²¹ reported the results of a study of the isolated gallbladder of the dog in which the gallbladder was intubated through the cystic duct and alterations in pressure recorded with a tambour. The results of these observers are in agreement with our own.

Higgins and Mann⁸ stated that "the moot question as to whether the gallbladder ever does empty its contents was definitely settled by Boyden in his studies on cats." Boyden¹⁰ is now convinced that the gallbladder empties its contents through the cystic duct as the result of muscular contraction. The former authors concluded that the gallbladder empties through the cystic duct by the contraction of its own intrinsic musculature, and that other factors are of minor, if of any, importance in this process.

The question as to whether or not respiratory movements are a factor in gallbladder emptying is not as yet definitely settled. Winkelstein and Aschner¹¹ expressed the belief that the intra-abdominal pressure at the height of inspiration is the major factor in evacuation of the gallbladder. We do not doubt that respiratory movements can cause the evacuation of some bile, but we believe that these are not major factors in the process.

Recently Graham¹² stated that although he was not willing to "ascribe to muscular contractions the exclusive rôle in this drama, perhaps we have not assigned sufficient importance to the factor of intrinsic contractions of the muscle."

Demel and Brummelkamp¹ and Halpert³ do not deny that some bile leaves the gallbladder by way of the cystic duct, but they deny that the amount is significant. Sweet,² on the other hand, definitely stated that what goes in the cystic duct never comes out by this route. In order to prove this, it remains for this group of workers to obtain definite evidence that all the bile constituents leave at a rate consistent with the absorption of water and sodium chloride. Of this we have not been able to obtain confirmatory evidence. This evidence will be published in a series of papers to come from workers in this laboratory. In the blood from the cystic vein of the dog or the lymphatics

²⁰ Lieb, C. C., and McWhorter, J. E. *J. Pharmacol. & Exper. Therap.* **7**: 83, 1915.

²¹ Ischiyama, F. *Mitt. a. d. med. Fak. d. k. univ. Kyushu Fukuoka* **10**: 61, 1925.

of the gallbladder of the cat or dog, we have not found bile pigment in concentrations that could be demonstrated by either the icterus index method of Meulengracht or the diazo method of van den Bergh, even though at the same or subsequent times we obtained evidence that substances such as sodium chloride or sodium iodide pass through the wall of the gallbladder. The pigment must be removed at a rate proportional to the other constituents of the bile or it tends to accumulate, as is evidenced by a comparison of the concentrations of pigment present in liver and in gallbladder bile in the same species. Even though we assumed that there is a threshold for the absorption of bilirubin, judging from the concentration of pigment consistently found in gallbladder bile, we would expect to find the pigment in even greater concentration in the lymph or blood from the gallbladder.

CONCLUSIONS

1 Data are presented which show that, under the conditions of the experiment (isolation), the gallbladder of the dog, guinea-pig and monkey shows rhythmic contractions and responds to stimulation by drugs.

2 We have failed to find certain constituents of the bile in the lymphatics or blood vessels draining the gallbladder.

3 We have observed contractions of the human gallbladder in a patient whose respiration was temporarily checked.

4 From these experiments we are led to conclude that although certain constituents of the bile leave the gallbladder by the lymphatics or blood vessels, concentrated bile leaves the gallbladder by the cystic duct as a result of contraction of the gallbladder.

THE NERVE PATHWAYS IN THE VOMITING OF PERITONITIS *

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A careful review of the literature has failed to disclose any explanation of the mechanism of vomiting in peritonitis which is supported by experimental facts. No recorded attempt by critical experiment to determine the nature of the emetic stimulus and to discover its manner of action could be found, although the phrase "peritoneal irritation" was noted in practically every work on peritonitis and vomiting. The present study was undertaken because of the apparent lack of proof that vomiting in peritonitis is really due to irritation of the peritoneum.

Since the most important subjective evidence on which the interpretation and diagnosis of acute peritoneal inflammation are based consists of the history of abdominal pain, nausea and vomiting, any contribution that leads to a better understanding of the origin and nature of the symptoms is of direct interest to the clinician.

Although the emetic stimulus has usually been considered to be a nervous impulse, it was thought possible that it might be either a hormone or a toxin carried in the blood. Since emesis is induced by the direct application to the vomiting center of minute amounts of certain normal constituents of the blood, such as choline and histamine, it is possible that when one of these is present in the blood in an increased amount, it may cause nausea and vomiting. In intestinal obstruction, which frequently complicates peritonitis, histamine may be present in the blood in abnormally large amounts, and, in such cases, may possibly constitute the stimulus to vomiting.

It is believed that observations recently made in this laboratory tend to exclude the probability of either a toxin or a hormone providing the important emetic stimulus in peritonitis. For example, in a series of fifteen normal cats, intraperitoneal injection of 10 cc of a 50 per cent turpentine emulsion produced vomiting within six seconds after the injection, a reaction time which seemingly would preclude

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a chemical stimulation of the center and yet be entirely within the limits of a reflex phenomenon. Furthermore, as will be described shortly, peritonitis failed to produce vomiting in six cats in which the vagus nerves had been divided in the thorax and the abdominal sympathetic and splanchnic innervation destroyed.

If the emetic stimulus is a nervous impulse, the three possible pathways to be considered are the vagi, the sympathetics and those cerebro-spinal nerves which also supply the peritoneum, namely the phrenics, the lower six thoracics, the iliohypogastrics and the ilio-inguinal nerves.

The method of study has been as follows. A twenty-four hour bouillon culture of *B. coli* was injected intraperitoneally into each of twelve normal cats and seven normal dogs, and was found in every instance to produce a fatal peritonitis, the duration of life varying from five to twelve days. Without exception, vomiting was a constant feature of the disease. These animals served as controls.

Twelve other cats that had received similar injections and that had also been subjected to bilateral low intrathoracic vagotomy performed from sixty to seventy-two hours after injection vomited as did the controls and failed to differ in this respect from animals in which the vagi were intact.

Bilateral abdominal sympathectomy and splanchnotomy was performed in five cats. In these animals peritonitis similarly induced by *B. coli* produced vomiting which did not differ in either character or frequency from that seen in the controls.

In five dogs suffering from a colon bacillus peritonitis, the spinal cord was transected at the level of the second thoracic vertebra. Vomiting was feeble thereafter, as the innervation of the abdominal muscles was destroyed, but was definitely present and persistent.

Six cats were first subjected to a bilateral low intrathoracic vagotomy and allowed to recover. Two weeks later, the abdominal sympathetic chains were resected and the splanchnic nerves divided. After one week of convalescence, an intramuscular injection of lobeline sulphate (0.003 mg. per kilogram) was given, and prompt emesis resulted in each instance, demonstrating the integrity of the efferent emetic mechanism. Peritonitis was next induced in these animals by *B. coli*. In this series a striking result was obtained. Every animal died within six days, and postmortem examination revealed in each instance a frank purulent general peritonitis, the diagnosis being confirmed by microscopic section. Yet not one of the six animals vomited even once during the course of the disease.

PROTOCOL

EXPERIMENT 27 (cat 154)—Dec 23, 1929 Lobeline sulphate, 0.003 mg per kilogram of body weight, was injected intramuscularly followed in two minutes by emesis

December 24 Under intratracheal ether insufflation, the pleural cavity was opened through the tenth interspace (right), the right lung was collapsed and packed away with gauze. The anterior and posterior vagal cords were exposed on the lower part of the esophagus and sectioned. The lung was expanded by obstructing expiration, and the thoracic wall closed in layers. This procedure required fifteen minutes.

December 28 The animal was up and about, eating in apparently normal fashion. Lobeline sulphate, 0.003 mg per kilogram, was injected intramuscularly followed by prompt emesis.

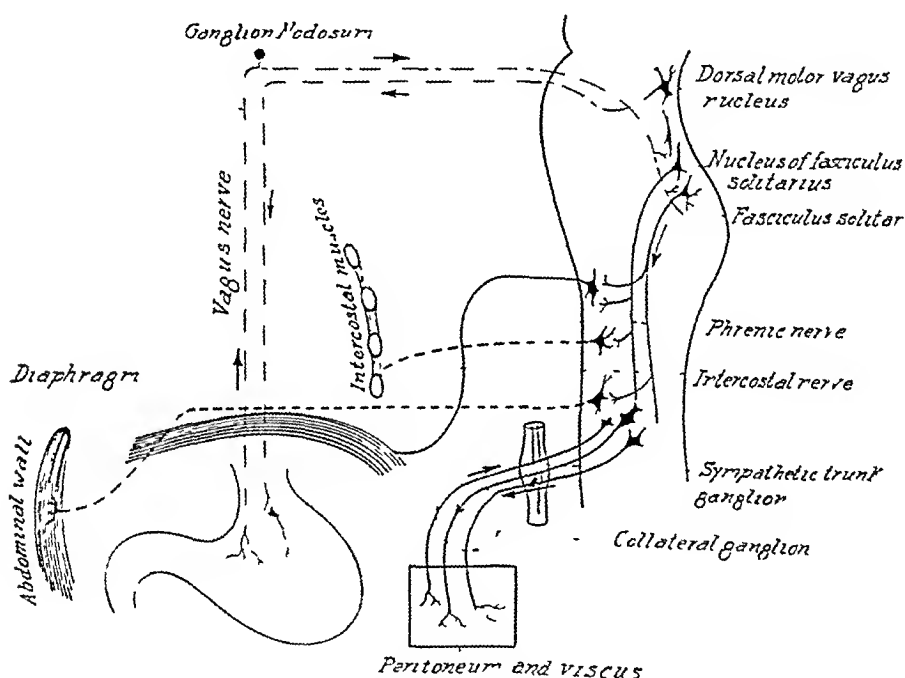


Diagram of the nerve pathways involved in the vomiting produced by peritonitis

Jan 3, 1930 Under intratracheal ether insufflation, through a midline abdominal incision, the peritoneal cavity was opened, and the stomach and intestines were brought out and wrapped in warm moist towels. The left major splanchnic nerve was identified at the point of its entrance to the semilunar ganglion and sectioned. The left abdominal sympathetic trunk was identified, followed through the diaphragm and sectioned in the lower part of the thorax, then sectioned caudally to the level of the paired ganglions just below the sacral promontory, its minor splanchnic branches being sectioned as exposed. A similar procedure was repeated on the right side. The intestines were replaced, and the abdominal wall was closed in layers.

January 8 The animal was up and about eating in apparently normal fashion. Lobeline sulphate, 0.003 mg per kilogram, was injected intramuscularly, followed promptly by emesis.

January 9 Twenty cubic centimeters of a twenty-four hour bouillon culture of *B coli* was injected intraperitoneally

January 16 The animal died of diffuse, suppurative peritonitis confirmed by autopsy and microscopic examination of tissue The animal did not vomit during the course of its disease

Obviously these animals were able to vomit, as demonstrated by the injections of lobeline sulphate The emetic stimulus was present, as evidenced by all of the animals previously observed In these animals, then, the emetic action of the peritoneal inflammation had been effectively abolished by the operative procedure, namely, by vagotomy and sympathectomy

In resume, in each of forty-six animals in which either the vagus mechanism or the abdominal sympathetic mechanism or both were intact, vomiting was a prominent accompaniment of peritonitis In each of six animals in which both vagal and sympathetic paths were destroyed, no instance of vomiting was recorded, although the peritonitis was uniformly fatal It would seem then that colon bacillus peritonitis produced vomiting through a local irritation of afferent nerve endings and not through toxic or humoral changes The afferent emetic impulse from the peritoneum to the medullary centers evidently traverses only vagal or sympathetic paths, since in the absence of these paths, although cerebrospinal nerves (including the phrenic nerves) are still active, emesis fails to occur Since the destruction of only one of these paths, i e, the vagal or the sympathetic, fails to abolish the vomiting of peritonitis, it would appear that the afferent emetic impulse traverses either path with equal facility This observation is in line with that of Hatcher and Weiss,¹ who found that afferent emetic impulses produced by large oral doses of mercuric chloride ascend over either the vagi or the sympathetics, depending on the integrity of the tract

COMMENT

From an anatomic and physiologic point of view, there are several factors that apparently enter into the mechanism of vomiting irrespective of the causative one Some are partially understood and have been confirmed by experimental evidence, others are indefinite and hypothetical In the foregoing experiments, we have dealt with the vomiting of peritonitis and have found it to be reflex rather than toxic A brief summary of our knowledge of the nervous mechanism concerned with the vomiting act would perhaps be of interest

¹ Hatcher, R A and Weiss, Soma Studies on Vomiting J Pharmacol & Exper Therap 22 139 1924

Although Giannuzzi² was apparently the first to suggest the existence of a vomiting center, Thumas³ has received the credit for discovering the so-called "center." Forty years ago he described an area lying on both sides of the midline of the floor of the fourth ventricle, the destruction of which with a blunt instrument prevented the emetic action of apomorphine chloride. Much of this older work has been superseded by the careful work of Hatcher and Weiss,¹ who found that the sensory nuclei of the vagus nerves were essential to vomiting in cats. They could not produce emesis after destruction of the sensory nuclei, but they did produce emesis by the application of minute amounts of apomorphine chloride (0.0001 mg.) to the nuclei before destruction. Their explanation of Thumas' failure to produce emesis after destruction of this area is that vomiting cannot be induced when the center is depressed by mutilating operative procedures in its vicinity. In our own laboratory it was found that lobeline sulphate and apomorphine chloride did not produce emesis in either cats or dogs after the floor of the fourth ventricle had been traumatized.

Faradic stimulation of either of the cut ends of the vagus nerves does not regularly induce vomiting (McCrea, McSwiney and Stopford⁴ have recently reviewed the literature in this regard). Furthermore, Laughton⁵ found that while faradic stimulation of the dorsal vagal nucleus of the cat produces contractions of the hypotonic stomach, no emesis resulted. In this connection we have methodically faradized the floor of the fourth ventricle of cats and dogs and have been unable to produce vomiting. Obviously, neither the sensory nucleus of the vagus nerve nor its motor nucleus is per se the vomiting center. However, drugs as employed by Hatcher and Weiss apparently do exert a selective action on certain cells somewhere in the region of the sensory nucleus of the vagus nerve, and thus initiate the sequence of coordinated muscular phenomena that constitute the vomiting act. That faradization has not produced this effect is not necessarily contradictory evidence, for so specific a response may readily fail to appear in the widespread reaction to gross electrical stimulation.

2 Giannuzzi, G. Untersuchungen über die Organe welche an dem Brechact theilnehmen und über die physiologische Wirkung des Tartarus stibiatus, *Centralbl f d med Wissensch* **3** 1, 1865.

3 Thumas, L. J. Ueber das Brechcentrum und über die Wirkung einiger pharmakologischer Mittel auf dasselbe, *Arch f path Anat u Physiol* **123** 44, 1891.

4 McCrea, E. D., McSwiney, B. A., and Stopford, J. L. B. The Effect on the Stomach of Section of the Vagus Nerves, *Quart J Exper Physiol* **16** 195, 1926.

5 Laughton, N. B. The Effects on the Stomach of the Stimulation of the Dorsal Vagus Nuclei, *Am J Physiol* **89** 18, 1929.

Hatcher⁶ pointed out the relative importance of a center in the brain to coordinate vomiting. Some species of mammals vomit while others, chiefly the herbivora, do not. The fact that herbivora do not even try to retch under the influence of emetics suggests that they lack a well developed vomiting center.

It is yet a question whether it is actually justifiable to speak of a vomiting center, but as Alvarez⁷ aptly put it, "it is certainly convenient to so designate that area in the brain which is essential to the vomiting process in that it receives afferent emetic impulses, discharges efferent ones and coordinates in an orderly sequence the various movements and inhibitions necessary for emesis such as closure of the pylorus, contraction of the lower part of the stomach, relaxation of the fundus, cardia and esophagus, closure of the glottis, stoppage of the respiration, stimulation and inhibition of the diaphragm and stimulation of the abdominal muscles."

Apparently there is some central coordinating mechanism concerned with the vomiting act, since the vomiting induced by an emetic, for example, is indistinguishable objectively from that induced by other causes. The muscles concerned and the efferent nerves do not vary with the causative or afferent impulse, and the discussion of the efferent paths resolves itself into a consideration of the innervation of these muscles.

The diaphragm, which plays an active rôle in vomiting, is supplied by the phrenic nerve. In the embryo, the diaphragm is a derivative of the cervical myotomes that are displaced posteriorly as the diaphragm descends to its permanent level. These myotomes carry down in their descent branches of the third, fourth and fifth cervical nerves. These branches fuse into the phrenic nerve and contain both motor and sensory fibers. It has been reasoned that the motor fibers continue their function in activating the diaphragm, while the sensory fibers through disuse, may cease to register localized sensations in the diaphragm. However, these afferent fibers retain their ability to carry impulses to the cervical cord as is seen in referred pain in the cervical region following strong stimulation of the central end of a cut phrenic nerve. Although there is indisputable evidence that the sensory fibers do function in the phrenic nerve, work has been presented in this article as evidence that the afferent emetic impulses they carry are negligible if present.

The abdominal muscles, which form the most important group of voluntary muscles, receive their nerve supply from the lower six

6 Hatcher, R. A. *The Mechanism of Vomiting*, *Physiol. Rev.* 4:479, 1924.

7 Alvarez, W. C. *The Mechanics of the Digestive Tract*, ed. 2, New York, Paul B. Hoeber, Inc., 1928.

thoracic, the ilio-inguinal and the iliohypogastric nerves—typical “mixed” cerebrospinal nerves. Although Moritz⁸ found that the voluntary muscles of the abdomen in man can exert a pressure on the stomach equal to a column of water 3 meters high, Gold in Hatcher’s laboratory caused vomiting in a cat in which the abdominal muscles had been severed longitudinally and transversely so that it was impossible for either them or the diaphragm to compress the stomach. Vomiting in a modified fashion was produced in this laboratory in animals with paralysis of the abdominal muscles. Moreover, one of us recently observed a child of 4 months with congenital absence of the abdominal muscles who vomited in an apparently normal fashion.

The vagal parasympathetic fibers carry efferent impulses to the stomach and intestines, although the active part these organs play in the vomiting act is secondary. That the stomach is not essential for the vomiting act was probably first demonstrated by Magendie’s⁹ classic experiment in which he replaced a dog’s stomach with a pig’s bladder and produced vomiting. Even more striking, however, is the work of Eggleston and Hatcher,¹⁰ who saw typical movements with the expulsion of a considerable volume of frothy mucus from the esophagus following the extirpation of the stomach and intestines with the cardia tied. Rost¹¹ stated that men and women often vomit after total gastrectomy.

The sympathetic fibers presumably carry efferent emetic impulses. However, this pathway would appear relatively unimportant in the light of experiments which have been detailed, for it was found that after section of the splanchnics and abdominal sympathectomy, the efferent emetic mechanism in cats was apparently not disturbed, as every animal vomited after the intramuscular injection of lobeline sulphate. Similarly, Hatcher and Weiss¹² observed that the emetic action of a peripheral emetic such as mercuric chloride was not inhibited when the spinal cord was sectioned at the level of the second thoracic vertebra. Results paralleling these were obtained by us in dogs with peritonitis which vomited although the spinal cord had been severed at the same level.

8 Moritz. Studien über die motorische Thätigkeit des Magens. I. Mitteilung ueber das Verhalten des Druckes im Magen, *Ztschr. f. Biol.* **32** 313, 1895.

9 Magendie. Memoire sur le vomissement, 1813, quoted by Hatcher (foot-note 6).

10 Eggleston, C., and Hatcher, R. A. The Seat of the Emetic Action of Apomorphine, *J. Pharmacol. & Exper. Therap.* **3** 551, 1912.

11 Rost, F. The Pathologic Physiology of Surgical Diseases, trans. by S. P. Reimann. Philadelphia: P. Blakiston’s Son & Company, 1923.

12 Hatcher, R. A., and Weiss, Soma. The Seat of the Emetic Action of the Digitalis Bodies, *Arch. Int. Med.* **29** 690 (May) 1922.

As regards the parasympathetics, Hatcher and Weiss found that after a large oral dose of mercuric chloride, section of the vagi in the neck failed to inhibit emesis. In like manner, in our experience the vomiting of cats and dogs was not affected by intrathoracic section of the vagi.

Exner and Schwarzmunn¹³ reported twenty cases of gastric crises in which there apparently was no abnormality in the vomiting mechanism following bilateral vagotomy. Latarjet, Schiassi and Mayo¹⁴ have performed similar neurectomies without disturbing the vomiting mechanism.

That the efferent impulse is a nervous impulse has been shown by the fact that transection of the cord at the level of the second thoracic vertebra and bilateral vagotomy in the same animal followed by the injection of apomorphine chloride evoke practically no retching response in the dog, although the diaphragm can be felt to contract in a normal fashion.

The possible anatomic pathways for afferent impulses arising from peritoneal irritation include the lower six thoracic nerves, the ilio-inguinal, the iliohypogastric, the phrenic and the vagus nerves and the general visceral afferent fibers which traverse the sympathetic trunks. The peritoneum lining the abdominal wall receives its innervation from the seventh to the twelfth thoracic, the ilio-inguinal and the iliohypogastric nerves, which are cerebrospinal mixed nerves. The peritoneal surface of the diaphragm likewise receives some fibers from these intercostal nerves and also from the ramifications of the phrenic nerve, which is in reality a "displaced" branch of the cervical plexus and a cerebrospinal mixed nerve. Thus, the sensory nerve supply of the entire parietal peritoneum is derived from somatic elements. The visceral peritoneum, on the contrary, is supplied by the vagus and sympathetic nerve trunks, which contain afferent fibers belonging to the visceral rather than to the somatic group. This distinction seems to be significant in view of the results of experiments performed in our laboratory. Differential denervation of the peritoneal surfaces as previously detailed, indicates that there are only two afferent pathways for emetic impulses in peritonitis, namely, the vagal and sympathetic trunks. In animals with the phrenic and other cerebrospinal

13 Exner, A., and Schwarzmunn, E. Gastrische Krisen und Vagotomie, *Mitt a d Grenzgeb d Med u Chir* **28** 15, 1914.

14 Latarjet, A. Resection des nerfs de l'estomac. Technique operationnelle, resultats cliniques, *Bull Acad de med* **137** 681, 1922. Schiassi, B. The Role of the Pyloro-Duodenal Nerve Supply in the Surgery of Duodenal Ulcer, *Ann Surg* **81**:939, 1925. Mayo, C. H. Division of the Vagi for Pylorospasm, *Ann Surg* **88** 669, 1928.

nerves intact subjected to a bilateral abdominal sympathectomy, splanchnotomy and bilateral intrathoracic vagotomy, peritonitis did not cause vomiting. Since in these animals the innervation of the parietal peritoneum was still intact, it seems reasonable to conclude that only the visceral afferent fibers are of importance in the reflex vomiting act, and that it is irritation of the visceral rather than of the parietal peritoneum that causes vomiting in peritonitis.

The apparent localization of the afferent emetic pathways in the vagus and sympathetic nerves and the exclusion of the cerebrospinal nerves from such a system are rather striking in the light of clinical observation as expressed by Weiss and Davis¹⁵ "That the relief of pain is due to blocking of cutaneous afferent impulses and that the infiltration with novocain does not exert an indirect influence on the visceral afferent sympathetic impulses is shown by observations on patients who aside from visceral pain also suffer from nausea and vomiting due to the same cause as the pain." In these patients the skin infiltration abolished pain at once, but the vomiting persisted. The persistence of vomiting after blocking of the pain fibers (cerebrospinal) indicates that strong visceral afferent impulses continue to reach the high centers through the sympathetic and vagal chains.

SUMMARY

The experiments here reported show that the vomiting of peritonitis is the result of the stimulation of afferent nerve endings located in the peritoneum.

The emetic impulse thus initiated passes to the medullary center by way of sensory nerve fibers which are included in both the vagal and sympathetic trunks. Section of these trunks prevents the occurrence of vomiting in peritonitis, although phrenic and other cerebrospinal nerve paths are left undisturbed.

Since by sympathectomy alone or by vagotomy alone vomiting in peritonitis is not abolished, the afferent emetic impulse evidently traverses either pathway with equal facility.

The consensus among anatomists seems to be to the effect that the parietal peritoneum is chiefly supplied by cerebrospinal somatic afferent nerves whereas the visceral peritoneum receives its supply from the visceral afferent fibers that course in the vagal and sympathetic trunks. If this point of view is correct, the foregoing experiments indicate that it is the irritation of the visceral and not of the parietal peritoneum that gives origin to the vomiting in peritonitis.

¹⁵ Weiss, Somer and Davis, David. The Significance of the Afferent Impulse from the Skin in the Mechanism of Visceral Pain. *Am J M Sc* **176** 517, 1928.

PANCREATIC CYSTS

REPORT OF FORTY-SEVEN CASES

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Few clinical studies of large series of cysts of the pancreas have been reported in the literature, and only brief attention has been paid to the pathologic changes of this disease. Of 723,397 patients admitted at the Mayo Clinic, eighty-eight with cyst of the pancreas have been operated on. One of us,¹ in 1921, reported forty-one cases from the clinic, the largest original series recorded up to that time. This paper includes a review of the literature and a clinical survey, with comment, of the forty-seven patients treated surgically at the clinic since the report in 1921. A study of the etiology and pathology of this disease will be presented elsewhere.

Morgagni,² in 1761, described multiple cysts on the pancreas, mesentery and omentum in a cadaver. Claessen,³ in 1842, reviewed a series of cases from the literature. "The treatment (of cysts of the pancreas) must be of the symptoms as they arise and by diet," wrote Friedreich,⁴ in 1875, in the first basic monograph on the subject. As early as 1862, Le Dentu⁵ punctured a cyst of the pancreas and drained it, in the belief that it was a cyst of the liver. Peritonitis developed, and the patient died. "Cysts of the pancreas," he wrote, after this experience, "should be relegated to the list of those affections where the healing art is impotent."

* Submitted for publication, May 16, 1930

+ From Division of Surgery, the Mayo Clinic

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2 Morgagni, G B. The Seats and Causes of Diseases, London, A. Millar and T. Codell, and Johnson and Payne, 1909, vol 5, p 578

3 Claessen, H J. Die Krankheiten der Bauchspeicheldrüse, Köln, M. Du Mont-Schauberg, 1842, pp 368

4 Friedreich, N. Cysts of the Pancreas in von Ziemssen, H. *Cyclopaedia of the Practice of Medicine*, New York, William Wood & Company, 1878, vol 8 p 615

5 Le Dentu, M. Rapport sur l'observation precedente, *Bull Soc anat de Paris* 10 197 (March) 1865

Lucke,⁶ in 1866, drained a cyst of the pancreas, the patient died. Bozeman,⁷ in 1881, extirpated a cyst successfully. The next year, Gussenbauer,⁸ a pupil of Billroth, made a tentative diagnosis of cyst of the pancreas before operation and devised a method of drainage whereby he sewed the parietal peritoneum to the skin, and the walls of the cyst to the parietal peritoneum. Marsupialization became, and has remained, a standard surgical procedure.

There followed detailed studies of individual cases of cyst by Fenger,⁹ W J Mayo,¹⁰ Osler,¹¹ McBurney,¹² Senn,¹³ and others. Experimental work was done by Senn¹⁴ and Thiroloix.¹⁵ Such studies were reviewed in monographs by Korte,¹⁶ Lazarus,¹⁷ and Oser,¹⁸ and much of our present knowledge is based on them.

The body of the pancreas lies behind the stomach. It is on a level with the first lumbar vertebra and on the boundary between the peritoneal and retroperitoneal spaces. The cyst makes its way toward the anterior parietal peritoneum in the line of least resistance. Hence, its

6 Lucke, A., and Klebs, E. Beitrag zur Ovariectomie und zur Kenntnis der Abdominalgeschwulste, *Virchows Arch f path Anat* **41** 1 (Nov) 1867

7 Bozeman, N. Removal of Cyst of Pancreas Weighing Twenty and One-Half Pounds, *M Rec* **21** 46 (Jan 14) 1882

8 Gussenbauer, Carl. Zur operativen Behandlung der Pankreascysten, *Arch f klin Chir* **29** 355, 1883

9 Fenger, Christian. A Case of Traumatic Cyst of the Pancreas, *Chicago M J & Exam* **66** 74, 1888

10 Mayo, W J. Pancreatic Cyst. Uretero-Vaginal Fistula, the Result of Vaginal Hysterectomy. Successful Reimplantation of Ureter into the Bladder, *M Rec* **45** 168 (Feb 10) 1894

11 Osler, William. Lectures on the Diagnosis of Abdominal Tumors. Lecture V. Tumors of the Intestine, Omentum and Pancreas, Miscellaneous Tumors, *New York M J* **59** 545 (May 5) 1894

12 McBurney, Charles. Cyst of the Pancreas, *Ann Surg* **19** 492, 1894

13 Senn, Nicholas. The Surgical Treatment of Cysts of the Pancreas, *Am J M Sc* **90** 17 (July) 1885, The Surgery of the Pancreas, As Based Upon Experiments and Clinical Researches, *ibid* **93** 121 (Jan) 1887, *Experimental Surgery*, Chicago, W J Keener, 1889, p 379

14 Senn, Nicholas. The Surgery of the Pancreas, as Based on Experiments and Clinical Researches, *Am J M Sc* **92** 141 (July) 1886

15 Thiroloix, J., quoted by Oser (footnote 18)

16 Korte, W. Die chirurgischen Krankheiten und die Verletzungen des Pankreas, *Deutsche Chirurgie*, Stuttgart, Ferdinand Enke, 1898, pp 234

17 Lazarus, Paul. Beitrag zur Pathologie und Therapie der Pankreaserkrankungen mit besonderer Berücksichtigung der Cysten und Steine, *Ztschr f klin Med* **51** 203, 1904

18 Oser, Leopold. Diseases of the Pancreas, in Nothnagel. *Encyclopedia of Practical Medicine. Diseases of the Liver, Pancreas and Suprarenal Capsules*, Philadelphia, W B Saunders Company 1903, p 180

ultimate relations are influenced by the point of origin in the gland, the reflection of the peritoneum, and the arrangement of the overlying viscera. Most frequently, the cyst presses into the lesser peritoneal cavity and presents between the stomach and the transverse colon, and behind the gastocolic omentum (fig 1). The next most common site

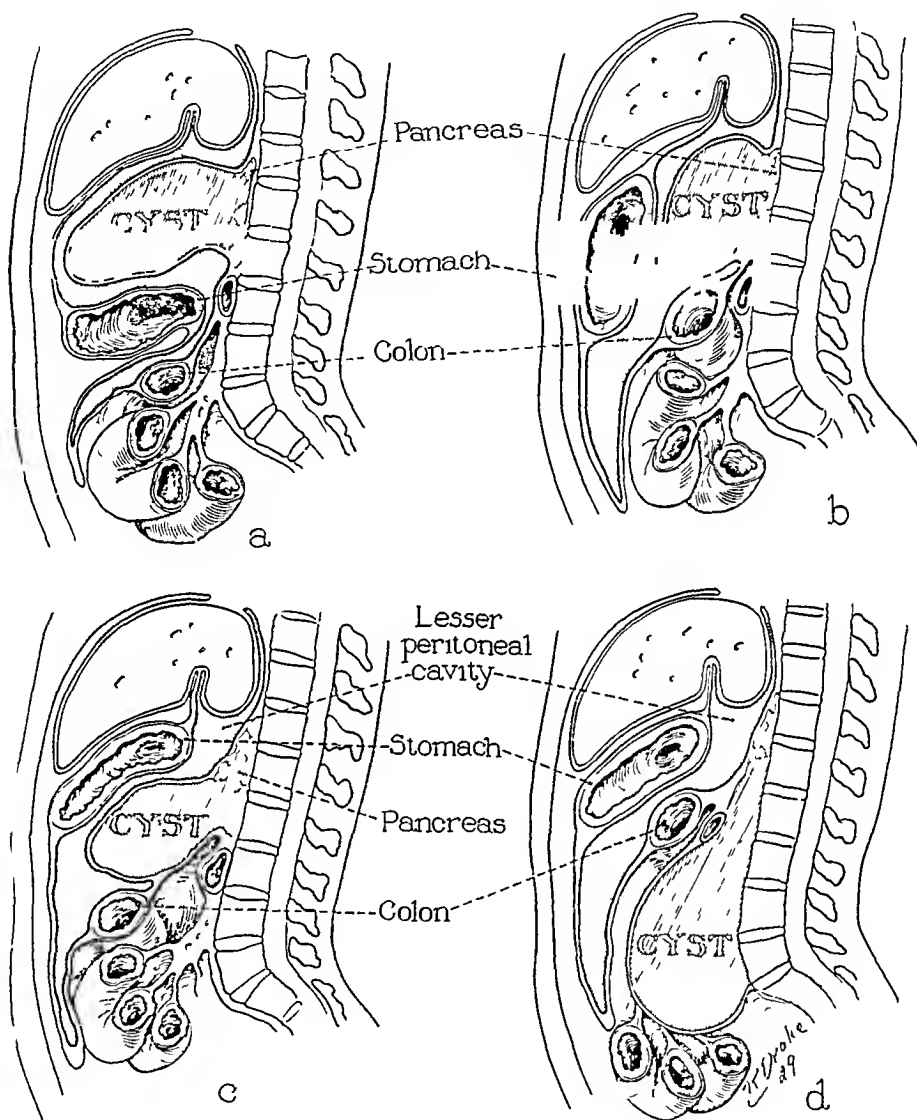


Fig 1—The relations of cyst of the pancreas to abdominal viscera. The most common site is exemplified in *c*, next in frequency are the situations shown respectively in *a* and *b*. The situation shown in *d* is very infrequent.

is between the stomach and the liver or protruding into the lesser peritoneal cavity behind the stomach (fig 1 *a* and *b*). However, the cyst may invaginate itself between the layers of the mesocolon, and when it does this it usually presents behind the transverse colon. Anatomic-

cally, the layers of the transverse mesocolon separate along the pancreas and cover its anterior surface. The cyst will rarely cause bulging of the inferior surface of the transverse mesocolon downward and forward, and so will lie below the colon, as in the cases reported by Hersche¹⁹ and others. In one of the cases in our series, the cyst was found in the pelvis, between the layers of the mesocolon of the sigmoid. Martin²⁰ reported finding a cyst of the pancreas directly behind the descending colon. The cyst may burrow toward the pelvis wholly retroperitoneally, as in the case reported by Hulke²¹. A cyst reported by Primrose²² had burrowed behind the posterior parietal peritoneum.

Most important in the recognition of cysts of the pancreas are the character and situation of the mass. A smooth, relatively immobile hemispheric swelling, with tense walls, is characteristic. In most of the cases, such a swelling is in the upper part of the abdomen between the ensiform cartilage and the umbilicus, in the median line or to the left of it. In forty-five of the forty-seven cases, more than 95 per cent, a tumor was felt above the umbilicus. In twenty-one cases, it was to the left of the median line, in eleven, approximately in the median line, and in thirteen, to the right of the median line. In one case, the tumor was felt in the pelvis and was found to be enclosed in the mesentery of the sigmoid. A mass was felt in one hundred and fourteen of Korte's one hundred and twenty-one cases which were reviewed from the literature, in forty-eight cases the mass was in the median line, in forty, it was situated to the left, and in ten it was situated to the right of the median line, in sixteen cases, the mass appeared below the level of the umbilicus.

Cyst of the pancreas, as a rule, is relatively immobile. When it is situated in the tail of the gland, and without adhesions, it may be freely movable. Mobility was noted in eleven of the cysts in our series. Nine of the mobile cysts were found to originate in the tail of the gland. In two cases, the point of origin was not given. Respiratory movements will be felt when the cyst is in contact with the diaphragm, or when pressure is transmitted from the diaphragm. Five cysts were noted as moving with respirations. Of this number, two

19 Hersche, J. Operation einer Pankreascyste von seltener anatomischer Lagerung, *Wien klin Wchnschr* 5 727 (Dec 22) 1892.

20 Martin, A. Ein Fall von Pankreascyste, *Virchows Arch f path Anat* 120 230 (May) 1890.

21 Hulke. Pancreatic Cyst, in *Reports of the Clinical Society of London*, *Lancet* 2 1273 (Dec 3) 1892.

22 Primrose, A. Pancreatic Cysts and Pseudocysts. Report of a Case of Total Extirpation by an Extraperitoneal Method, *Surg Gynec Obst* 34 431 (April) 1922.

were found next to the liver and two were very large. The percussion note is deadened where the tumor is most prominent, in the periphery, an intestinal percussion note can be demonstrated. A zone of tympanic percussion usually is found between the cyst and the liver. Palpation and percussion in various positions of the body will help to clarify the relation of the mass to abdominal organs.

The appearance of the mass is the most important objective symptom. Twenty-four of the forty-seven patients complained of a mass in the abdomen. Three of this number described it as fulness. In the majority of cases, the mass developed gradually. However, in one instance it was noticed three days, and in another six days, after an accident.²³ One patient said the mass appeared over night. Another patient complained of a feeling of pressure in the epigastrium, but only when the stomach was filled with food. Payr²³ cited a case in which the tumor disappeared and recurred three times in two months. The cyst described by Hersche fluctuated in size. Two of the patients in our series gave a history of disappearance of the mass. In one of the two, a cystadenocarcinoma was found.

Pain is the most important of the subjective symptoms of cyst of the pancreas. Forty-three of the forty-seven patients (91 per cent) complained of pain. Studies concerning the incidence of pain in patients who have only cyst of the pancreas are not available in the literature. Disease was found in other organs in nineteen cases in our series. In thirteen cases, choleliths were present, and in three, gross evidence of cholecystitis only was found. More than 34 per cent, therefore, gave evidence of cholecystitis, as compared to 41 per cent of the series reported by Judd in 1921. Gross evidence of pancreatitis was found in four cases, in one of which pancreatic stones were present. In one case, the pancreatitis was found together with cholelithiasis. Pancreatitis was found with duodenal ulcer and appendicitis in another case. Necrosis of abdominal fat was found in one case of pancreatitis. In twenty-eight cases, only cyst of the pancreas was found, twenty-four of these patients, more than 85 per cent, complained of pain. The four cases classed as malignant and probably malignant were in this group. In thirteen cases, the pain was in acute attacks. In eleven cases, the pain was more or less steady. Four patients with cyst only did not complain of pain, although two in this group said they had indefinite abdominal distress. A malignant cyst was found in one of the four cases.

²³ Payr Erwin. Pankreaszyste seltene Topographie, Operation und Heilung. Wien klin Wchnschr 11 629 (June 30) 1898.

Cholecystitis and pancreatitis are frequently associated with cyst of the pancreas and must be considered in evaluating the symptoms of this disease. Organs in the upper part of the abdomen are in intimate association. The frequency of cholecystic disease in cyst of the pancreas indicates that cysts of the pancreas, following inflammatory manifestations in the upper part of the abdomen, probably are only obvious residual signs of a process which has involved not only the pancreas, but adjacent organs as well.

Of the associated symptoms, influence on the general health, jaundice and nausea and vomiting are significant. The general health was affected severely in most of the cases in our series. Loss of weight and weakness were two of the most common symptoms. In nineteen of the forty-three patients who had unquestioned benign cyst, there was no loss of weight. In twenty-nine of the total number of forty-seven cases, the losses ranged from 4 to 60 pounds (1.8 to 27.2 Kg). Seventeen patients lost less than 25 pounds (11.3 Kg), and twelve lost more than 25 pounds (11.3 Kg). Of the two patients with malignant cysts, one lost 10 pounds (4.5 Kg) in three months and the other lost 17 pounds (7.7 Kg) in a year. Of the two patients with cysts which were probably malignant, one lost 10 pounds (4.5 Kg) in two weeks and the other lost 20 pounds (9.0 Kg) in four months. Nausea and vomiting were common complaints.

In ten cases there was a definite history of jaundice. In three other cases, the history of jaundice was doubtful. Of the thirteen cases, cholecystitis with stones was present in three, and a thickened gallbladder in two. Jaundice was said to be caused by pressure of the cyst on the common bile duct in nine of one hundred and twenty-one cases which were reviewed by Korte. Excess fat in the stools was found in only two cases in our series. In one case, stones were present in the duct of Wirsung, and in the other case the wall of the gallbladder was thick. In three cases there was a history of diarrhœa. Evidence of cholecystitis was found in two of the three cases and there was a history of jaundice in one of the two. In three cases, the patients gave a history of having passed clay-colored stools. In one case, only a cyst was found. In one case of cyst of the pancreas and chronic cholecystitis with stones the patient had had spells during which tarry stools were passed. In eighteen cases the patients complained of constipation. Unilateral hematuria in a case reported by Ransohoff²⁴ was found to be due to pressure of the pancreatic cyst on the left renal vein.

24 Ransohoff Joseph. Pancreatic Cyst as a Cause of Unilateral Hematuria, with Report of a Case. *Tr. South Surg. & Gynec. A.* 28:119, 1915.

The interval between onset of first symptoms and the patient's admission in our series varied from two weeks to twenty years. Five patients gave a history of symptoms extending over a month or less. Twenty-five of the forty-seven patients, more than 53 per cent, gave a history of less than twelve months' duration. Hulke saw a patient who apparently had had a cyst for forty years. Sensations of epigastric distress, weight and fulness early in the disease were complained of.

There were twenty-eight women and nineteen men in our series. The age distribution is shown in the tabulation. In Korte's one hundred and twenty-one cases reviewed from the literature, there were sixty men and fifty-six women. Sex was not specified in five cases. Thirty-six cases occurred in the fourth decade and thirty in the third decade. Of the patients who had benign cysts in our series, the youngest was 20 and the oldest 72 years of age. Railton²⁵ reported a case in an infant aged 6 months. Two of the forty-seven cysts were proved to be malig-

Age Distribution by Decades of Patients With Cyst of the Pancreas

Decade	Cases	Benign	Malignant	Probably Malignant
Third	11	11		
Fourth	9	7	2	
Fifth	12	12		
Sixth	9	9		
Seventh	5	3		2
Eighth	1	1		
Total	47	43	2	2

nant at necropsy. Two were classified only as probably malignant because microscopic confirmation was lacking.

With a rapidly rising tumor of the epigastrium following acute inflammatory conditions, cyst of the pancreas becomes a probability. Cyst of the ovary, mesenteric and omental cyst, cyst of the liver, hydrops of the gallbladder, cyst of the suprarenal capsule, fluid tumor of the kidney, retroperitoneal tumors, cyst of the posterior gastric wall, cyst of the spleen, and aneurysm, may have to be considered in differentiation. Large cysts of the pancreas are reported in the literature as being mistaken frequently for ovarian cyst. The uterus is in its normal position, usually, when cyst of the pancreas is present, and it is possible to palpate the ovary in most cases, in cases of large ovarian cyst, the uterus is more likely to be pushed to the side of the pelvis. The patient may aid the differentiation of ovarian and pancreatic cyst by relating that the mass grew from above downward or from below upward.

²⁵ Railton T C. A Case of Pancreatic Cyst in an Infant, *Brit M J* 2 1318 (Oct 31) 1896

Moynihan²⁶ stated that mesenteric cysts are characterized by prominence of the tumor near the umbilicus, great mobility, especially transversely, possibility of rotation about a central axis, and the presence of a belt of resonance across the cyst. A cyst of the omentum usually is very mobile. However, if it arises directly below the greater curvature of the stomach, such a cyst may give signs and symptoms identical with cyst of the pancreas.

Hydatid cyst of the liver may cause hemispheric bulging in the epigastrium. A band of resonance separates a pancreatic cyst from the liver in typical cases and aids in differentiation. In giant hydrops of the gallbladder, the dulness of the tumor and of the liver is nearly always continuous. The hydrops will have axial mobility unless restrained by adhesions. Suprarenal cysts are less common than cysts of the pancreas, Moynihan stated that they enlarge most commonly above the transverse mesocolon. However, they may grow between the layers of the transverse mesocolon. Obviously, distinction from cysts of the pancreas is impossible with such relations.

Fluid tumors of the kidney, such as hydronephrosis, cysts and pyonephrosis, usually are ruled out by the history and urograms. Retroperitoneal sarcomas may present similarity to cysts of the pancreas but are nonfluctuant unless cystically degenerated. Retroperitoneal cysts and cysts of the posterior gastric wall may take the same line of growth as cysts of the pancreas, and distinction is hardly possible. An area of resonance usually separates cyst of the pancreas from the spleen, and distinguishes it from splenic cyst. A cyst of the pancreas which lies over the aorta may be confused with aneurysm. Expansile pulsation is absent in a cyst. Abscesses of the pancreas arise rapidly and are more sensitive to pressure than cysts. Total necrosis gives rise to much more severe symptoms. In summary, differential diagnosis may be restricted to ovarian, mesenteric, omental, splenic and hepatic cysts, hydrops of the gallbladder, fluid tumors of the kidney, retroperitoneal sarcomas and aortic aneurysm. Suprarenal and retroperitoneal cysts and cysts of the posterior gastric wall are indistinguishable from cysts of the pancreas, but are extremely rare.

Roentgen examination is a major aid in the diagnosis of cysts of the pancreas. A filling defect in the stomach which can be eliminated by displacing the stomach or displacement of the duodenum and small intestines points toward the diagnosis of cyst of the pancreas. An enlarged duodenal curve is characteristic of enlargement in the region of the head of the pancreas. Small cysts may be confused roentgenologically with benign tumors of the stomach. The stomach and colon

26 Moynihan B. G. A. Mesenteric Cysts. *Ann Surg* 26:1 (July) 1897.

have been dilated as an aid in diagnosis Gussenbauer called attention to this, and the method was used commonly before the advent of roentgen rays Diagnostic aspiration is dangerous and is of historic interest only The presence of a ferment in the cystic fluid is not diagnostic, for other fluids, such as ascitic fluid, the contents of ovarian cyst, and pleural exudates, have been found to contain starch-splitting ferments In many cysts of the pancreas, ferments are not to be found

Cyst probably was the first disease of the pancreas to be treated surgically Choice of operation depends on the size, variety, situation and condition of the cyst The ideal treatment is complete removal, if possible, because by such a procedure the inconvenience of prolonged drainage is obviated In the clinic the removal was not attempted except in carefully selected cases With such precautions there was little difference as to the risk and the ultimate outcome between removal and drainage A small cyst with few adhesions situated preferably in the tail of the pancreas with narrow pedicle usually should be extirpated In cases in which the cyst is large and adherent and in which the glandular tissue encroaches considerably on the cyst, marsupialization is the method of choice

Seven of the forty-seven cysts in this series were excised completely Most of these cysts measured from 6 to 10 cm in diameter One cyst of a diameter of 20 cm was removed Thirty-three of the cysts were marsupialized and drained in one stage The cyst is drained by a puncture with a needle, and the aperture is clamped The peritoneum covering the cyst, and the parietal peritoneum, are sutured, the cyst is opened, and a rubber catheter and sometimes iodoform gauze are introduced In some cases the cyst was packed Sometimes a purse string suture was applied about the drainage tube Total excision was carried out in seven cases, in all of which the cysts were benign Partial excision and drainage was done in six cases Exploration only was done in one case, in which the cyst was malignant Epithelial lining usually is absent from the cyst Judd advocated destroying such a membrane mechanically, when one is present Schwyzer²⁷ applied tincture of iodine to the interior of the cyst Primrose sewed the posterior parietal peritoneum to the anterior parietal peritoneum before opening the cyst Other procedures that have been used for cyst of the pancreas are aspiration, partial extirpation, anastomosis with the gallbladder, anastomosis with the jejunum and puncture of the cyst with subsequent roentgen treatment Schwyzer used the extra-peritoneal approach through a lumbar incision Peters²⁸ exposed a

27 Schwyzer, Arnold Discussion, *Minnesota Med* 4 82 (Feb) 1921

28 Peters, G A Hydatid Cyst of the Tail of the Pancreas, *Canad Pract & Rev* 26 75 1901

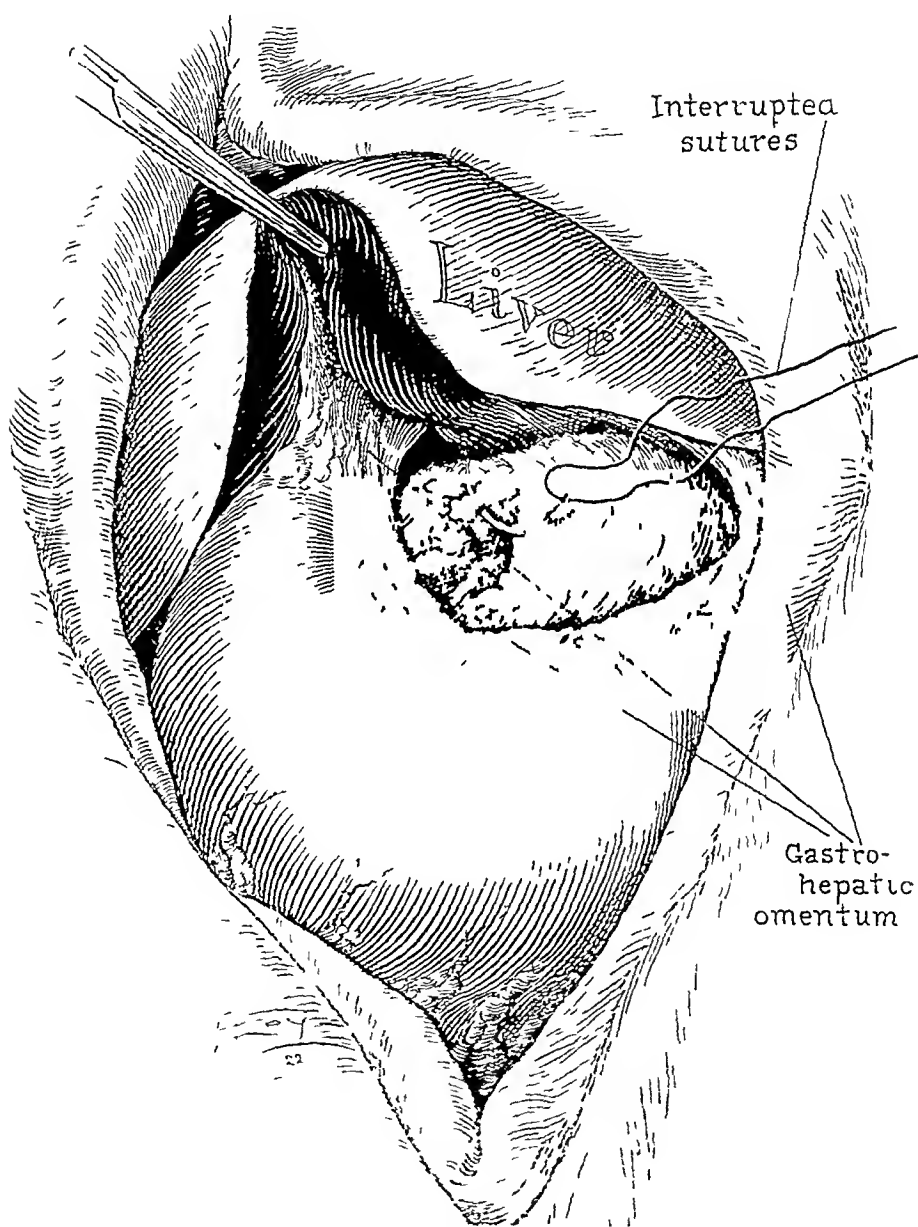


FIG 2—The first step in technic after resection of cyst

cyst in the tail of the pancreas by a left lumbar incision parallel to the last rib. Willis²⁹ excised a cyst which was adherent to the aorta and Kosin'ski³⁰ is said to have divided the pedicle of a cyst by cautery.

Dangers of allowing a cyst to remain, aside from the inconvenience to the patient, are probability of enlargement, threat of mechanical interference with other organs and the possibility of rupture.

Aspiration has been found dangerous and futile. It should not be thought of for diagnostic purposes. Moynihan stated that it should be considered only when the patient is ill from another disease and is suffering so acutely from pressure that the tension must be relieved in order to prepare the patient for laparotomy. In one case in our series scars of repeated aspirations, done elsewhere than at our clinic, were noted below the umbilicus.

Diabetes mellitus was present in three of the cases in our series. In one case the urine contained 1.33 Gm. of sugar per hundred cubic centimeters at the time of operation, but the urine was free from sugar a year later.

Persistent discharge from the fistula made by drainage may become a troublesome complication. Kerr³¹ reported a case in which the fistula had drained for fifteen years. From 500 to 600 cc. of secretion was discharged daily from a fistula in a case of pancreatic cyst reported by Cushing³². Culler³³ treated two patients with roentgen rays to hasten closure. Hamilton³⁴ used radium in a fistula of a pancreatic cyst. Gutierrez³⁵ transplanted a fistulous tract from the pancreas into the stomach. The wound healed rapidly and the patient recovered. After marsupialization in our series the discharge persisted a few weeks, sometimes a few months, following which the patient did not complain further of symptoms referable to the cyst. In one case the cyst was drained twice. In a few instances, the wound continued to dis-

29 Willis, A. M., and Budd, S. W. Pancreatic Cysts with Report of a Case, *Surg. Gynec. Obst.* **20** 688 (June) 1915.

30 Kosin'ski, J. Annotations. The Pancreatic Juice in the Human Subject, *Lancet* **1** 948 (April 25) 1891.

31 Kerr, A. A. Cysts and Pseudocysts of the Pancreas, with Report of Cases, *Surg. Gynec. Obst.* **27** 40 (July) 1918.

32 Cushing, H. W. Traumatic Rupture of the Pancreas. Formation of Hemorrhagic Cyst, Operation, Followed by Pancreatic Fistula and Recovery, *Boston M. & S. J.* **138** 429 (May 5) 1898.

33 Culler, R. M. Cure of Pancreatic Fistula by the Roentgen Ray, *J. A. M. A.* **75** 20 (July 3) 1920.

34 Hamilton, C. S. Prolonged and Profuse Postoperative Drainage of Pancreatic Cyst and Use of Radium, *Surg. Gynec. Obst.* **35** 655 (Nov.) 1922.

35 Gutierrez, A. Implantation into the Stomach of a Pancreatic Fistula Following Cyst, *Internat. Abstract Surg.* **43** 214 (Sept.) 1926.

charge for as long as a year, and rarely for as long as two years. Boric acid ointment, collodion, or other protective substance has been spread over the skin about the wound. If the wall does not contain an epithelial lining, the cyst fills in gradually with granulation tissue. In our series, no patients returned to the clinic with sinuses that had drained for more than two years.

SUMMARY

A clinical analysis is presented of forty-seven cases of cyst of the pancreas in which operation was done at the Mayo Clinic in the past ten years. The tumor was felt above the umbilicus in more than 95 per cent of cases. Cholecystic disease was present in more than 34 per cent. More than 85 per cent of the patients in whom only cyst of the pancreas was found complained of pain. Nine of eleven cysts noted as being mobile were found to originate in the tail of the gland. With careful selection of cases for extirpation there was little difference as to risk and ultimate result between extirpation of the cyst and drainage.

UNDESCENDED TESTIS

PRINCIPLES AND METHODS OF TREATMENT *

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Undescended testis is a condition frequently seen by the surgeon, especially the genito-urinary surgeon. As the condition is generally noted early in life by anxious parents, the patients are soon brought for expert opinion and advice, a fortunate occurrence, as practically all such afflicted children are thus seen by the medical profession early enough to escape permanent testicular damage incident on long delay in surgical correction.

Observers have differed regarding the incidence of this condition. Marshall¹ of Edinburgh, on examining recruits for the British and conscripts for the French armies, reported in 1828 an incidence of 1.02 per cent among 10,800 men examined. Zeibert,² 1898, reported an incidence of 0.2 per cent in 6,962,543 examined in the Austrian army between 1870 and 1882. Bevan³ estimated the incidence at 1 in 500. The United States War Department⁴ reported 3.1 per thousand men examined for the draft, or an incidence of 0.31 per cent.

It has been a constant observation that cryptorchidism occurs most frequently on the right side. In Coley's⁵ group of cases, 238 were right-sided, 188 left-sided and 55 bilateral. Berger,⁶ reporting 116 cases, found one-half to be right-sided, one-fourth left-sided and one-

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1 Marshall, H. Hernia Among Recruits for the British and Conscripts for the French Armies, Edinburgh, 1828.

2 Zeibert, K. A. Ueber Kryptorchismus und seine Behandlung, Diss. Heidelberg, 1898.

3 Bevan, Arthur Dean. Operation for Undescended Testicle and Congenital Inguinal Hernia, *J A M A* **33** 773 (Sept 23) 1899, *The Surgical Treatment of Undescended Testicle*, *ibid* **41** 718 (Sept 19) 1903, in Keen. *Surgery*. Philadelphia, W. B. Saunders Company, 1908, vol 4, p 592, *Arch f Klin Chir* **72** 1035, 1904, *Tr Am Surg A* **47** 314, 1929.

4 Defects Found in Drafted Men, Draft Record, War Department, U S A 1920.

5 Coley, W. B. Operative Treatment of Undescended Testis with Reference to End-Results, *Surg Gynec Obst* **28** 452 1919.

6 Berger, P. L'ectopie testiculaire de l'adulte. *Rev gen de clin et de therap* **22** 12, 1908.

fourth bilateral In our group, the left side was found to be most often afflicted

The etiology of undescended testis is by no means a closed chapter. Many theories to explain this condition have been advanced. Some of them are as follows

1 According to one theory, undescended testis is caused by conditions associated with the gubernaculum testis, such as paralysis of its muscle fibers, faulty attachment to the testis or even absence of gubernaculum

2 Another theory is that the abnormality is caused by obstruction to the normal descent in the inguinal canal by either narrowing of the entire canal or stenosis of the external ring. This theory suffers badly when one considers that in many cases of cryptorchidism the testis can be drawn up into the inguinal canal readily by the mere force of the cremasteric reflex

3 Another theory, interesting but difficult to believe, is that adhesions occur between the peritoneum and the testis, epididymis or spermatic cord. Some even go so far as to ascribe these adhesions to fetal peritonitis

4 The length of the spermatic vessels has been given consideration by some as a cause. Observers have constantly noted shortness of the vessels and many have laid the blame there, but it has been suggested that this shortness is a result rather than a cause

5 Turner⁷ of Guy's hospital, in 1925, propounded a theory that faulty position of the fetus in utero causes abnormal pressure of the thigh against the inguinal canal and prevents complete descent of the testis into the scrotum

Others have suggested that abnormalities of the testis or of the epididymis are responsible. The hereditary factor has also come in for its share of blame

That any single cause is a constant etiologic factor is difficult to believe. Certain it is, however, that in operations for this deformity the shortness of the spermatic vessels offers the greatest obstacle to placing the testis in the bottom of the scrotum

The undescended testis is generally found to be somewhat smaller and of softer consistency than normal. Accompanying indirect inguinal hernia of some degree is the rule, though this is not true in all cases. As previously mentioned, the spermatic vessels are always short and generally bound down by fascial bands and adhesions, their length determining the level at which the testis lies. The vas on the other hand, is found to be of normal and adequate length, and in arrested

⁷ Turner, P. Analysis of Results in Fifty Cases of Transseptal Orchidopexy for Imperfectly Descended Testicle. Guy's Hosp. Rep. 75: 209, 1925

testes sometimes loops down out of the external ring into the scrotum. We have observed several such cases. The scrotum, while it varies considerably in size, often gives the appearance of being rudimentary. This appearance has led some observers to believe that failure of scrotal development plays an etiologic rôle. Observation of operative cases leads one to a contrary opinion.

All undescended testes eventually undergo morphologic and functional change. Hunter,⁸ in 1791, pointed out that the abdominally retained testis was probably more defective than those arrested along the inguinal canal. Recent investigations by numerous observers, most notably Crew,⁹ Fukui,¹⁰ and Moore,¹¹ have amply borne out this early observation. The work of Moore of Chicago is of more than passing interest in this connection. During the past ten years this investigator has done a tremendous amount of research work on animals of all types, and has definitely established the fact that elevation of temperature is the essential factor in retarded testicular development in cryptorchidism. Some of his experiments will bear citing. On progressively shortening the scrota of sheep and goats until the testes eventually lay flush against the body, progressive degenerative changes in the testes were noted so far as spermatogenesis was concerned. Likewise, experimental cryptorchidism, of both the abdominal and inguinal types, brought about these changes. He further established his thesis by ingeniously insulating the scrotum against loss of heat by radiation, and here again produced the same changes. On returning the testes to their normal scrotal position in the operative cases, and on deinsulating the others, he was able further to observe a return to normal spermatogenesis. Confirmatory evidence was also obtained by direct application of heat to the laboratory animals' genitalia for varying periods of time.

The morphologic changes within the undescended testis have been observed repeatedly, and observers are in agreement as to these changes. Briefly summarized, the accepted views are as follows:

8 Hunter, John. *Observations on Certain Parts of the Animal Economy*, ed 2, London, 1792, p 1.

9 Crew, F A E. A Suggestion as to the Cause of the Aspermatic Condition of the Imperfectly Descended Testis, *J Anat* 56 98, 1921-1922.

10 Fukui, A. On a Hitherto Unknown Action of Heat Ray on Testicles, *Japan M World* 3 27, 1923.

11 Moore, Carl R. Cryptorchidism Artificially Produced, *Proc Am Soc Zool*, *Anat Rec* 24 383, 1922-1923, On the Relationship of the Germinal Epithelium to the Position of the Testis, *ibid* 25 142, 1923, The Behavior of the Testis in Transplantation, Experimental Cryptorchidism, Vasectomy, Scrotal Insulation and Heat Application, *Endocrinology* 8 493, 1924. Moore and Chase. Heat Applications and Testicular Degeneration, *Anat Rec* 26 344, 1923. Moore and Oslund. Experimental Studies on Sheep Testis, *Anat Rec* 26 243, 1923. Moore and Quick. The Scrotum as a Temperature Regulator for the Testis, *Am J Physiol* 68 70, 1924.

1 The further the preadolescent testis has descended in its normal route, the more normal does it appear histologically

Cooper,¹² in a gland at the external inguinal ring in an adult male, found parts showing complete spermatogenesis. Hobday¹³ found spermatogenesis in testes that remained in the lower part of the inguinal canal, but in those found in the upper part of the canal or abdomen this was rare. Bland-Sutton¹⁴ found, however, one case showing complete spermatogenesis in an abdominal testis.

2 The younger the age at which a retained gland is examined, the more nearly normal are its morphologic appearances.

Rawlings¹⁵ found that undescended testes in boys under the age of 10 years show no morphologic changes, but in those examined after puberty it could readily be seen that the organ had not undergone changes incident to puberty.

Odoirne and Simmons¹⁶ stated "testes though undescended are of normal structure during childhood but undergo none of the normal changes of puberty."

Cooper¹² found that cell differentiation and spermatogenesis began to develop at about the age of 11, and that at puberty the tubular cells began to show degenerative changes in the retained testis. Complete degeneration he found to be a slow process.

Bland-Sutton¹⁴ suggested that retained testes may show spermatogenesis for a time after puberty.

Beigel¹⁷ found active spermatozoa in the semen of a man, aged 22, with bilateral inguinal retention.

Odoirne and Simmonds¹⁶ demonstrated active spermatogenesis in an undescended testis of a man, aged 30.

3 The interstitial cells of Leydig are apparently not influenced by the abnormal situation of a retained testis. As a matter of fact, some observers have noted an overabundance of this type of cell in the undescended testis (Cooper¹²).

12 Cooper, E. R. A. *The History of the More Important Human Endocrine Organs at Various Ages*, New York, Oxford University Press, 1925. *Histology of the Retained Testis in Human Subjects at Different Ages and Its Comparison with Scrotal Testis*. *J. Anat.* **64**: 5, 1929.

13 Hobday, F. T. G. *Castration and Ovariectomy*, ed. 2, London, W. & A. K. Johnston, 1914.

14 Bland-Sutton, J. *The Value of the Undescended Testis*. *Practitioner* **84**: 19, 1910.

15 Rawlings, L. B. *The Surgical Treatment of the Incompletely Descended Testis*, *Practitioner* **81**: 250, 1908.

16 Odoirne, W. B., and Simmons, C. C. *Undescended Testicle*. *Ann. Surg.* **40**: 962, 1904.

17 Beigel. *Virchows Arch. i. path. Anat.* **38**: 144, 1867.

From these established facts, one can safely say first, that orchidopexy had probably best be performed before the age of 9, second, that even after puberty and including the third decade, the operation may save a gland capable of some spermatogenesis, and third, that on account of active interstitial cell development in these glands, orchidectomy should never be given consideration at any age.

The incidence of malignancy has been given wide study, with investigators coming to no complete agreement. The preponderance of evidence would seem to indicate a greater incidence in the abnormally placed group. Surely the normally placed gland, by reason of its accessibility, will give evidence of abnormality earlier in event of malignant change than the abnormally placed one. We have felt that this alone should offer sufficient reason for performing orchidopexy at any age.

The earliest recorded orchidopexy was described by Rosenmeikel,¹⁸ in 1820. This operation consisted merely of fixation of the testis to the fundus of the scrotum with a suture. Since that day about thirty different methods have been devised. Of these, a few bear mention as showing some variation in principle of procedure.

(1) Fixation of the testis to the fundus of the scrotum by various means, with further feature of a purse-string at the scrotal neck.

(2) Various types of traction by thread, wire or elastic stretched between the testis and the thigh, perineum, heel or wire frame.¹⁹

(3) By fixation to the thigh, such as in the Torek method.²⁰

(4) By transplantation within the scrotum into the opposite scrotal sac, as in the Ombredonne operation.²¹

The first type has the objectionable feature of the purse-string above the testis, which may interfere with the circulation of the testis. The Bevan³ operation, which falls in this group, has the further objectionable feature of dividing the spermatic vessels in those instances in which complete descent is otherwise impossible. Bevan excused this procedure by stating that the deferential artery that accompanies the vas is sufficient to supply the testis. Experience has hardly borne out

18 Rosenmeikel. Ueber die Radicalcur des in der Weiche liegenden Testikels bei nicht vollendeten Descensus desselben, Munich, J. Lindauer, 1820.

19 Bidwell, L. A. A Modified Operation for the Relief of Undescended Testis, *Lancet* **1** 1439, 1893. Lanz. Der ektopisch Testikel, *Zentralbl f Chir* **16** 425, 1905. Delbet, P. De l'ectopie testiculaire et de son traitement par la fixation cutanee prepubienne du testicule. *Assoc franç de chir* **19** 754, 1906.

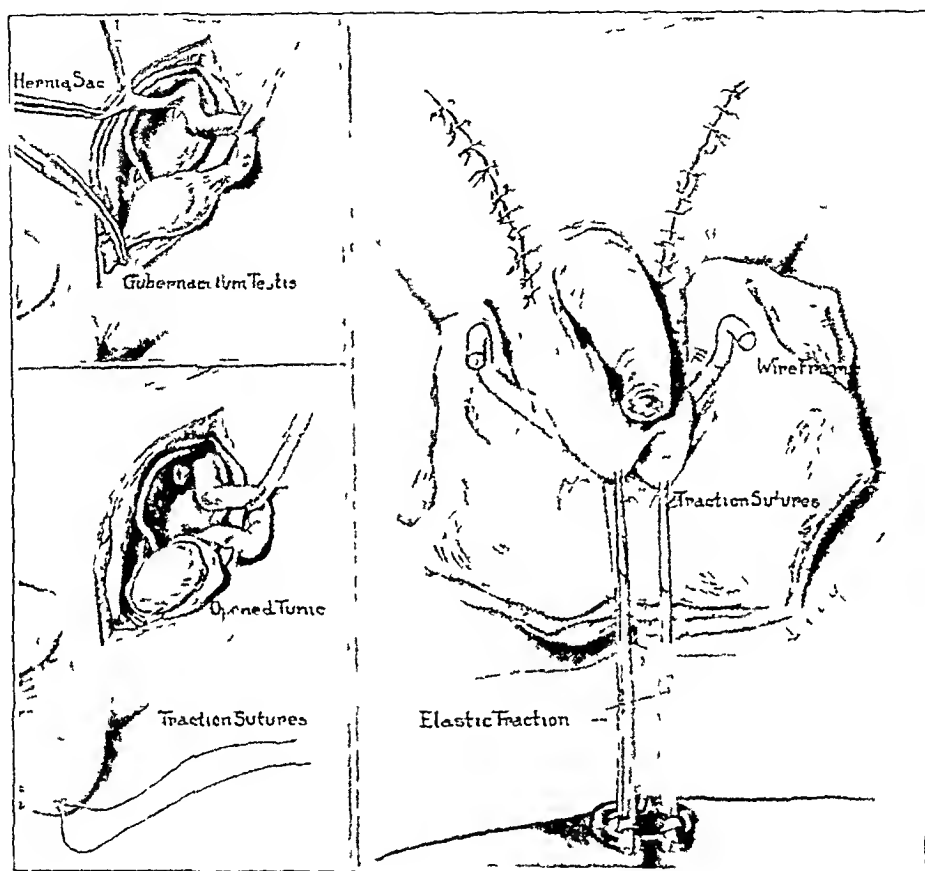
20 Torek, F. *New York M J* **90** 948, 1909. Meyer, H. W. Undescended Testicle, *Surg Gynec Obst* **44** 53, 1927.

21 Ombredonne, L. L'orchidopexie chez l'enfant, *Gaz méd de France* **2** 118. 1928. Higgins and Welti. Surgical Treatment of Undescended Testis, *Surg Gynec Obst* **48** 536, 1929.

this assertion²² The Torek method of fixation to the thigh as well as the transscrotal orchidopexy offer the objection that they are formidable procedures and applicable only in cases in which complete descent of the testis can be obtained

TECHNIC

During the past two years at the University Hospital clinic, a method utilizing the principle of constant traction has been employed A skin incision is made from 2 to 3 inches (5 to 7.6 cm) in length, extending from the internal inguinal



Operative procedure

ring down to the neck of the scrotum The inguinal canal is opened in the usual manner, the external ring being incised The testis and cord are then exposed and isolated The processus vaginalis is next dissected carefully from the cord structures and dealt with as any indirect inguinal hernial sac When a complete hernial sac is found, we think it unwise to close the lower end of the processus vaginalis as hydrocele is almost certain to follow The cord structures are now freed up to the internal ring from the many fibrous bands that are found to be surrounding them and producing much of their apparent shortening With one finger in the retroperitoneal space, the spermatic vessels are freed from the posterior surface of the peritoneum The cord structures will now be found to permit a fairly normal descent of the testis A finger is next pushed down into

22 Mixer Undescended Testicle in Children Boston M & S J 75 63 1916

the scrotum to establish a bed in which the testis is to lie. A long catgut suture with a straight needle at each end is then passed through the remains of the gubernaculum at its lowest point and tied so that the two ends can be used for traction on the testis. The needles are then introduced into the scrotum and pushed out through the skin at the lowest point, about 0.5 cm apart. With the sutures so placed, the testis is drawn well down into the scrotum. The sutures are then attached to a wire frame and rubber band so as to produce constant gentle downward traction on the testis. The inguinal incisions are next closed by any method that will give greatest length to the cord. The traction thus applied is left on for about twelve days, being adjusted occasionally during that period so as to remain constant. It has been found in many cases in which the testis can only be brought down to just outside the external ring at operation, that after a few days of such elastic traction the testis descends well down into the scrotum.

RESULTS

The principle involved in this technic is simple, the obtaining of permanent lengthening of vessels by continuous stretching. Our observations have seemed to prove this point satisfactorily.

In this regard, one case of our series is of particular interest. In a patient 9 years of age in whom the left testis was found to lie at the internal ring, it was brought down by dissection and subsequent traction to just outside the external ring. Eight months later he was reoperated on. On this occasion it was possible to bring the testis down to the midscrotal region, and twelve days after operation, when the traction was removed, the testis was in its normal scrotal position and has so remained after twelve months.

We feel that this simple two-stage operation is definitely indicated in those cases in which complete reposition cannot otherwise be obtained without cutting the spermatic vessels.

In our series of twenty-five cases here reported covering a two-year period, six were found to be bilateral, thirteen left-sided and six right-sided. The youngest person operated on was 3 years of age, the oldest 19.

Of the cases here reported we have been able to secure recent data on seventeen. Among these the testis is in the normal scrotal position in ten instances, and in the upper part of the scrotum in seven, in none was it at a higher level. In thirteen the testes are reported as being of normal size, two slightly larger than normal, one slightly smaller than normal and one definitely atrophic.

As this procedure has been used for only two and one-half years, one cannot, of course, give end-results. That will take time. Our post-operative results have thus far been satisfactory and we recommend this procedure as safe, simple and apparently physiologic.

FORTY-FOURTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY -

PHILIP D WILSON, M D

LLOYD T BROWN, M D

M N SMITH-PETERSEN, M D

AND

JOHN G KUHN, M D

BOSTON

RALPH K GHORMLEY, M D

ROCHESTER, MINN

MURRAY S DANFORTH, M D

PROVIDENCE, P I

GEORGE PERKINS

LONDON, ENGLAND

ARTHUR VAN DESSEL, M D

LOUVAIN, BELGIUM

AND

C HERMANN BUCHOLZ, M D

HALLF GERMANY

CONGENITAL DEFORMITIES

Congenital Torticollis—Using the sartorius muscles of the dog Middleton¹ repeated and confirmed Brook's experiments on the effects of ligation of artery and of vein, together and separately in respect to the production of ischemic necrosis. The results of these experiments led Middleton to believe that congenital torticollis was due to an ischemic contracture resulting from obstruction (during prolonged childbirth) to the venous return from the sternal head of the sternocleidomastoid muscle. His paper contained a colored photomicrograph of a section from a tumor of the sternocleidomastoid muscle in a child 4½ months of age which is almost identical with a section from the sartorius muscle in a dog eight weeks after ligation of the vein only.

[Ed. Note—The causation of congenital torticollis has never been satisfactorily explained. Middleton's studies throw new light on the

* This Report of Progress is based on a review of 266 articles selected from 486 titles dealing with orthopedic surgery appearing in the medical literature between Sept 15, 1930, and Jan 1, 1931. Only those papers which seem to represent progress have been selected for review.

1 Middleton D S. Brit J Surg 18 188 (Oct) 1930

subject, and point strongly to ischemic contracture as the etiologic factor. We hope that this work will be confirmed by additional investigation.]

Spina Bifida Occulta—Jelsma and Spurling² lamented the fact that relatively little had been written concerning spina bifida occulta. For this reason the true incidence of the condition was not known. It seemed fair to assume, however, that it was not uncommon, though many patients with this anomaly did not present symptoms. The clinical observations were divided into three main groups: the local signs, the neurologic manifestations and other anatomic anomalies. Operative treatment was the only method of cure, and this consisted in relieving pressure by the removal of a fibrolipomatous mass or by division of a fibrous membrane spanning the defect.

[ED. NOTE.—The point to be emphasized is that although spina bifida occulta is a common roentgenologic observation, it rarely gives rise to symptoms.]

Congenital Pseudarthrosis of the Tibia—Camurati³ defined congenital pseudarthrosis of the tibia as a localized dystrophy of the bone which might be associated with a similar lesion of the fibula. The total number of cases found by him in the literature was 118. At the Rizzoli Institute there were 27 cases in thirty-two years, or 0.98 per cent of the number showing congenital dislocation of the hip. There was a slight predominance of males in the series (57.62 per cent). The condition was rarely bilateral. Heredity did not play a part. A familial tendency was rare. Other congenital anomalies occurred in 11.03 per cent. Camurati believed that the condition was due to some embryonal change. He felt that glandular secretions (hypofunction and hyperfunction) and toxins might also play a considerable part in producing the change. The visible characteristic signs were deviation of the axis of the limb, atrophy of the leg, scar formation and vasomotor changes. A change in the size of the bone and, in some instances, abnormal mobility could be felt. The hip and knee were normal in their movements, the foot was limited in dorsal flexion.

The roentgenologic characteristics varied. In one type there was a curvature of the bone with atrophy of the diaphysis but thickening of the cortex at the site of the apex of the curvature, so that the medullary canal was lessened or obstructed. In the second type there was interruption of the continuity of the bone. In the third and most serious type there were marked changes in the ends of the bone at the site of the interruption, the ends being pointed and sometimes widely separated. Microscopic studies had rarely been made, and had yielded little definite information.

2 Jelsma, F., and Spurling, R. G. *Surg. Gynec. Obst.* **51**: 537, 1930.

3 Camurati, M. *Chir. d'org. di movimento* **15**: 1 (July) 1930.

The treatment in the second and third types, differentiated by roentgenograms, was either a massive bone graft or, in the second type, an osteoperiosteal graft. Immobilization of the bony surfaces in strict contact was essential. The prognosis was uncertain, but in one group (not the author's) of 97 cases cure was obtained in 30 cases, 6 of which were of the most grave type. Of the cases studied by the author improvement was obtained in 16, or 23.8 per cent, while in 51 cases no improvement was noted.

GROWTH DISTURBANCES OF BONE

Marble Bones—Pirie⁴ reported 5 additional cases of marble bones (Albers-Schonberg's disease). Four of these cases occurred in one family, the mother and three children. The author found that the earliest roentgenologic sign of this disease was a dense band at the end of the diaphyses. This was most commonly seen at the lower end of the femur and at the upper end of the tibia. A little later a certain amount of clubbing was seen at the ends of the long bones. The dense shadows extended more and more into the epiphyses and into the shaft of the bone. In the older cases dense shadows were seen in the carpal bones, most frequently the scaphoid. These dense shadows were distributed irregularly through the skeleton. If the disease was widespread throughout the skeleton, a certain amount of anemia occurred, owing to encroachment on the medullary cavity. Postmortem examination of such bones showed that the hardness was like that of chalk rather than that of marble. Microscopically the diaphyses showed calcified cartilage with irregular myeloid spaces. There were numerous small areas of ossification. No abnormality in the blood calcium or phosphorus was found. No fractures had occurred in these children. The author suggested a widespread infection as the cause of the disease.

Osteochondritis Juvenalis—Harbin and Zollinger⁵ discussed the various disturbances of growth centers known as osteochondritis, including the conditions known as Legg-Calve-Perthes' disease, Osgood-Schlatter's disease, Kohler's disease, etc. They pointed out that osteochondritis involved either the primary or the secondary centers of ossification and the various conditions were classified accordingly. The disease was self-limited, and usually healed spontaneously with or without deformity. It was felt that cases of coxa plana might in later years give rise to mechanical or traumatic arthritis. To obtain physiologic rest during the acute state, immobilization was advised for as long as from four to six weeks. When it was possible to dispense with plaster, some other form of apparatus might be used to prevent

4 Pirie, A. H. Am J Roentgenol 24 147 1930

5 Harbin M. and Zollinger, R. Surg Gynec Obst 51 145 1930

deformity until the active growth of the ossification center was completed. It was stated that while the cause of the condition was unknown, direct or indirect trauma usually played an important part.

[ED NOTE—We question whether it is often necessary to employ immobilization even in the acute stage of this condition. The disease is frequently symptomless, and we do not believe that any evidence has been adduced to show that its course can be modified by treatment.]

CALCIUM METABOLISM AND METABOLIC DISTURBANCES OF BONE

Calcium Requirements of the Body—In an editorial⁶ appearing in the *Journal of the American Medical Association* it was stated that calcium constituted about 1.5 per cent of the body—amounting to nearly 3 pounds (1.3 Kg.) in the adult male. Of this, over 99 per cent was present in the bones. The bones provided a ready source of calcium which had a far greater “mobility” or freedom of liberation and transport than was generally suspected. The best estimates currently available suggested the advisability of a daily intake of 1 Gm. or more of calcium in order to prevent loss of the indispensable element. Calcium was unevenly distributed in human foods, most food contained very little calcium. The cereal grains, tubers, meats, fish and fruits, all of which are prominent in the dietary of omnivorous man, were comparatively poor in calcium.

Vitamin D as a “calcium-mobilizing” factor was not a substitute for calcium. At birth the body had a low calcium content, and its normal development involved a large increase, not only in the amount, but also in the percentage that it contained, and so required a liberal supply of calcium in the food.

Milk was the best natural source of calcium. Recent investigations had proved that calcium was advantageously absorbed from most foods other than milk and also from artificial inorganic supplements of calcium to the diet. Healthy women who had ingested alternately milk and calcium lactate under otherwise comparable dietary conditions appeared to utilize the inorganic calcium as effectively as the calcium of the raw milk.

Calcium Metabolism in the Healing of Fractures—Bellelli⁷ studied the calcium and phosphorus content of the blood in 14 persons with fractures. He concluded that a study of the calcium curve was of some value in the convalescence from fractures. He found that the blood calcium diminished in 90 per cent of the cases during the first few days to between 2 and 2.5 mg. per hundred cubic centimeters of blood.

6 In Praise of Calcium editorial J. A. M. A. 95 1977 (Dec 27) 1930

7 Bellelli F. Riforma med. 46 966 1930

The calcium and phosphorus rose to values above the normal on the eighth or ninth day in young patients and on the seventeenth to the twentieth day in adults

Lewis⁸ studied 17 cases of fracture of the shaft of the long bones to determine whether the administration of viosterol had any effect on hastening union or callus formation. The amount of calcium and inorganic phosphorus of the blood was not materially raised, an average of 0.4 mg for the calcium and practically no change for the phosphorus were obtained. He concluded that the use of viosterol did not hasten union or callus formation in adults.

Administration of Vitamin D and of Phosphorus—Holmes and Pigott⁹ tested the antirachitic activity of six samples each of five brands of viosterol 100 D in comparison with samples of ergosterol without D and ordinary cod liver oil. It was found that the healing effect of the various samples of viosterol was far from standard, and that some specimens possessed much greater potency than others. This fact makes it difficult for the practitioner to estimate the proper dosage. They suggested that the use of cod liver oil, although necessitating larger doses, might be more satisfactory, for while viosterol has only an antirachitic factor, cod liver oil has this factor and is rich in vitamin A as well.

Compere¹⁰ studied the effect of phosphorus in 11 cases of severe rickets during the winter months. He found that while phosphorus given alone in doses of 1/100 grain (0.6 mg) twice daily had practically no effect on the rickets, its addition to cod liver oil hastened the healing of the rickets. The use of both cod liver oil and phosphorus cleared up the rickets more quickly than cod liver oil alone.

Influence of Parathyroid Gland—Speed and Rider¹¹ produced fracture in four dogs on which a thyroparathyroidectomy had been performed previously. Tetany was controlled by giving calcium lactate and thyroid extract. The low blood calcium and the imperfect and irregular healing of the fractures suggested to the authors that the calcium was directed away from the bones after parathyroidectomy.

Jaffe and Bodansky¹² produced changes in the long bones of growing puppies similar to those found in osteitis fibrosa cystica by injecting parathyroid extract (parathyroid extract-Collip) over long periods of

8 Lewis, K. M. *Ann Surg* **92** 415, 1930

9 Holmes, A. D., and Pigott, M. G. *New England J. Med* **203** 220, 1930

10 Compere, E. L. *Effect of Phosphorus in Rickets*, *Am J Dis Child* **40** 941 (Nov) 1930

11 Speed, K., and Rider, D. L. *Experimental Healing of Bone After Parathyroidectomy*, *Arch Surg* **21** 679 (Oct) 1930

12 Jaffe, H. L. and Bodansky, A. *J Exper Med* **52** 669 1930

time They believed that the changes produced were similar to those found in some patients with hyperparathyroidism, i. e., a negative mineral balance and decalcification of the skeleton

NEOPLASMS

Cysts in the Long Bones of the Hands and Feet—Platt¹³ reported a series of 20 cases of cysts of the long bones of the hand and the foot The bones involved, in order of frequency, were the proximal phalanges the metacarpals and, rarely, the metatarsals The cysts originated in the metaphysis The digit most commonly affected was the fifth finger The majority of the growths remained latent until discovered roentgenologically after local injury Incomplete spontaneous fracture occurred in half the patients Microscopic examination showed chondroma in 8 cases and osteitis fibrosa in 5 cases The author stressed the rarity of other types of bone tumors in the hands and feet, although in his paper he recorded an example of a giant cell tumor affecting the first metacarpal The differential diagnosis between chondroma and osteitis fibrosa could not be made on clinical or roentgenographic evidence, although it frequently was possible at operation, the myxochondroma exhibited a cavity filled with white, glistening, friable, granulating tissue and soft cancellous bone, and without any definite lining, the osteitis fibrosa cyst revealed a cavity that was empty or incompletely filled with fibrous tissue and that had a tough fibrous lining which peeled easily

Although spontaneous obliteration of an osteitis fibrosa cyst was known to occur frequently, Platt advocated operative intervention in all cases, owing to the difficulty of distinguishing between osteitis fibrosa and chondroma and the well known tendency of the latter tumor toward local malignancy In a young patient in whom roentgenograms show the cyst to have a thick-walled cortical boundary it might be worth while to postpone operation pending roentgen evidence of expansion of the cyst

The routine treatment at operation was to eradicate the contents by curettage, to cauterize the walls with pure phenol and to help obliterate the cavity by the insertion of an autogenous bone graft The author reported no failures after this type of operation, in every case the cyst had disappeared and had been replaced by bone

Articular Fibro-Endothelioma—Wagner¹⁴ reported 2 cases of a definitely encapsulated tumor arising from within a joint, one in a knee and the other in the anterior part of the ankle joint These were diagnosed as fibro-endothelioma

13 Platt H Brit J Surg 18 30, 1930

14 Wagner, L C Ann Surg 92 421, 1930

The diagnosis of this condition was difficult. There was swelling in only one part of the joint, and there was no particular tenderness or increase of synovial fluid. The range of motion was little affected, because the tumor was not in the articular or periarticular structures. Careful study of the roentgenograms with special attention to the structure of soft tissues was helpful. The treatment was surgical, and although a complete enucleation might be secured, the tumors were prone to recur. Roentgen treatment or Coley's toxin should be tried, but so far no cures had been reported. The tumors were removed as they recurred. Amputation of the affected extremity was usually necessary to effect a cure.

TUBERCULOSIS

Complement-Fixation Tests for Diagnosis—Wadsworth, Mattoner and Stevens¹⁵ performed complement-fixation tests for tuberculosis in 1,002 patients. Of 628 patients with pulmonary infection (supposedly tuberculosis) 546, or 86.9 per cent, reacted positively with at least one tubercle antigen. Of patients in whom acid-fast bacilli were recovered from the sputum 344, or 92.2 per cent, reacted positively. The serums in 40 cases of extrapulmonary tuberculosis were examined, 21, or 52.5 per cent, reacted positively. Of 314 patients with no clinical evidence of tuberculosis 44, or 14 per cent, gave a positive reaction. The author felt that the test was already of diagnostic value and that the reaction was proportional to the activity of the tuberculous process. The complement-fixation test in extrapulmonary tuberculosis gave too variable results to be of value.

Protective Vaccination—Calmette¹⁶ first vaccinated infants against tuberculosis in 1921. From that time until November, 1928, 116,180 infants had been so treated in France alone. He considered it a safe procedure. The duration of immunity was not accurately known, but the vaccination could be repeated without harm. In France the death rate for tuberculosis was 3.4 per cent for vaccinated, and 15.9 per cent for nonvaccinated infants.

Diagnostic Importance of Paravertebral Abscess—The diagnostic importance of the paravertebral abscess of Pott's disease was discussed by Rigler, Ude and Hanson.¹⁷ The differential diagnosis was also emphasized, the other important conditions to consider being osteomyelitis and mediastinal tumors. Various authors quoted by Rigler reported the presence of abscess in Pott's disease in from 20 to 66 per

15 Wadsworth, A. B., Mattoner, E. J., and Stevens, B. S. *Am Rev Tuberc* **22** 539, 1930.

16 Calmette, A. *M J & Rec* **132** 119, 1930.

17 Rigler, L. G., Ude, W. H., and Hanson, M. B. *Radiology* **15** 471, 1930.

cent of the cases. Often the abscess was the earliest roentgen sign and might appear before there was evidence of destruction of bone. This was true in 2 cases reported by the authors.

Nonoperative Versus Operative Treatment—Rollier¹⁸ reported the results of his method of treatment, which was a combination of heliotherapy, orthopedics and rational diet. The orthopedic treatment included rigorous maintenance of the horizontal decubitus, although it did not involve complete immobilization of the affected joint. The use of extension allowed of a cautious and gradual separation of the surface of the joint and avoided painful compressive ulceration. While maintaining relative immobility, it allowed small spontaneous movements of the joint which helped the deep circulation and hastened the healing of the foci in the bone and the regeneration of the cartilages. The fact that restoration of the cartilages occurred was, according to Rollier, clearly shown by the reappearance of the joint space in the roentgenograms, and it was this that explained the frequency with which movement and function were recovered.

Rollier reported the following end-results

	Hip	Knee	Foot
Cure maintained with function, per cent	74.0	66.4	92.6
Cure maintained with normal function, per cent	33.6	41.9	67.0
Cure maintained with partial function, per cent	66.4	58.1	25.0
Ankylosis, per cent	26.0	33.6	7.2

Lo Grasso,¹⁹ in discussing the nonoperative treatment of tuberculous joints of the lower extremity, stated that a patient with a tuberculous joint should be treated for the systemic infection and that the disease of the joint should be treated as a complication and not as the primary infection. He felt that operative procedures were likely to disseminate the disease if undertaken during the acute state. Surgical measures, if necessary, should be undertaken only after a preliminary course of conservative treatment in order to raise the resistance of the patient as much as possible. In his experience conservative treatment usually resulted in healing with useful motion of the joint and without recurrence of the disease.

Hibbs²⁰ reported on the operative fusion of tuberculous joints of the lower extremity. Fusion was obtained in all the joints operated on except in 11 cases of tuberculosis of the hip joint (8 per cent of 150 cases). There were 154 cases of tuberculosis of the hip joint, 18 cases of tuberculosis of the ankle joint and 4 cases of tuberculosis of

18 Rollier, A. J. Bone & Joint Surg. **12** 733, 1930.

19 Lo Grasso, H. J. Bone & Joint Surg. **12** 755, 1930.

20 Hibbs, R. A. J. Bone & Joint Surg. **12** 749, 1930.

the tarsal joints in which the operation was performed during this period of study. There had been no recurrence of the disease in any of the fused joints. The activities of the patients had not been limited by the operation. Because of the compensatory motion in the lumbar spine the patients whose hips had been fused were free from almost any handicap. The author felt that a great advantage of the fusion operation was that it freed the patients from the danger of extension of the disease from the focus in the joint as well as from long, uncertain treatment in hospitals or clinics.

[ED NOTE—The divergence between the nonoperative attitude, as exemplified by Rollier and Lo Grasso, and the point of view favoring surgical intervention, as represented by Hibbs, seems as wide as ever. Rollier's article is of importance in that for almost the first time he reports remote results, the sole criterion that should be employed in judging the results of treatment. These results are impressive, and no one employing similar methods in this country has been able to duplicate them. On the other hand, Hibbs reports remarkably good results from fusion operations, and these results can be duplicated by good surgeons anywhere. Taking into consideration economic, social, climatic and geographic factors in the United States, operative treatment seems to offer more in bringing about a cure than nonoperative treatment. We agree with Lo Grasso, however, that the patient must also be treated systemically for the primary infection and to arrest further extension of the disease, and that preferably such treatment should precede rather than follow operation.]

POLIOMYELITIS

Immune Serum Reactions—Aycock and Kramer²¹ tested the blood serums of 12 mothers and their infants for neutralizing substances against the virus of poliomyelitis. Ten of the mothers with their newborn infants neutralized the virus, as shown by intracerebral injection into monkeys. In 2 cases the virus was not neutralized. The authors felt that these observations pointed to a passive transmission of immunity from mother to infant.

In a recent editorial²² in the *Journal of the American Medical Association* the poliomyeliticidal action of normal human serum was discussed. The serum of persons who had recovered from poliomyelitis usually, though not invariably, had the power of killing, neutralizing or inactivating poliomyelitis virus in vitro. It was generally assumed, though

21 Aycock, W. L., and Kramer, S. D. *J. Exper. Med.* **52**: 457, 1930.

22 Poliomyeliticidal Action of Normal Human Serum, editorial. *J. A. M. A.* **95**: 1269 (Oct. 25) 1930.

without experimental proof, that this neutralizing power was a measure of the probable therapeutic value of such serums. Relatively few control tests had been made with normal human serums, the general assumption being that while the serums might occasionally neutralize poliomyelitis virus in vitro, they were usually inert or of such low viricidal power as to be of little or no therapeutic interest. Shaughnessey, Harmon and Bordon concluded from their investigation that serums from family contacts and normal children over 2 years of age possessed greater power to neutralize poliomyelitis virus than serums from persons who had recovered from an attack of the disease. Of even greater theoretical interest were the few tests made with serums from normal children under 2 years of age. Of the five serums from persons who had recovered from poliomyelitis thus far tested by the Chicago investigators none had neutralized virus in a dilution as high as 1:10. On the other hand, nearly 90 per cent neutralizations were obtained in 1:10 dilutions with the serums of normal children over 2 years of age. This observation suggested that in the normal infantile population immunization against poliomyelitis proceeded in much the same way as that against diphtheria.

PYOGENIC INFECTIONS

Reparative Process in Chronic Osteomyelitis—A study of the healing process in chronic osteomyelitis was made by Kreuscher and Hueper²³. In a series of 16 patients in whom the "saucerization operation" had been performed, tissue for study was obtained at varying intervals from the ulcerated region, including the epithelized border zone and superficial parts of the bone. In all cases evidence of a more or less advanced healing process was observed. In a few instances biopsies were performed repeatedly at intervals of from four to six weeks, beginning thirty days after the operation. The writers found that the bony defect was filled in by the production of three different zones of tissue formed in succession, namely, granulation tissue, strong fibrous and hyalinized connective tissue and loose connective tissue with lamellae of osteoid and osseous tissue. The presence of infection interfered to a greater or lesser extent with the proper formation and arrangement of these structures and therefore greatly retarded regeneration of bone. In the sections examined, no evidence of an attempt at formation of cortical bone was apparent. A loose, sometimes edematous connective tissue was present between the bony lamellae. In a single case there was an attempt at formation of cortical bone. In this instance complete epithelization of the defect had existed for six

23 Kreuscher, P. H., and Hueper, W. C. *J. Bone & Joint Surg.* 12: 541, 1930

months. The formation of cortex evidently occurred at a late period in bony regeneration. The same condition was found in regard to the formation of periosteum. Elastic tissue was only scantily present in the tissue covering the new-formed bone. The observations seemed to indicate that a prognostication of the postoperative healing process of chronic osteomyelitis from biopsy sections was possible, and that valuable information in regard to therapeutic management of the individual case might be obtained in this way.

ARTHRITIS

Classification, Causation and Treatment—The unusual interest that has recently been aroused in the study of chronic polyarticular arthritis is shown by the publication of symposia dealing with all phases of the subject, as well as by a number of articles of merit scattered throughout the medical literature.

Osgood²⁴ divided arthritis into two types according to the nomenclature of the American Committee for the Control of Rheumatism: atrophic and hypertrophic. The committee agreed that at the present time no single infectious agent, completely defined dietary deficiency or metabolic disturbance had been conclusively shown to be the sole cause of arthritis. The committee inclined to the belief that any one of these factors or certain combinations of them under appropriate circumstances might basically underlie the onset of the disease.

Swain²⁵ gave a résumé of seventeen years' experience in the treatment for arthritis. He found it helpful to divide the disease into infectious, atrophic and hypertrophic types. In the infectious type the removal of foci of infection and careful treatment with vaccines were efficacious after the general condition of the patient had been sufficiently improved. In the hypertrophic type the correction of the faulty body mechanics and the use of endocrine products as indicated offered most in treatment. He found a distinct hereditary tendency in the atrophic type. Here, no matter what the precipitating cause had been, the depleted physical condition, lack of resistance and metabolic instability were the factors that permitted the precipitating cause to become active. Early recognition and treatment of these underlying conditions would probably have prevented arthritis in a number of the patients.

Cecil²⁶ stated that the atrophic type of arthritis was, in the acute onset, secondary to a bacteremia. A preceding trauma to the joint or

²⁴ Osgood, R. B. Orthopedic Aspects of Chronic Rheumatism or Arthritis, J. A. M. A. **95** 992 (Oct. 4) 1930.

²⁵ Swain, L. T. J. Lab. & Clin. Med. **15** 1171, 1930.

²⁶ Cecil, R. L. J. Lab. & Clin. Med. **15** 1177, 1930.

a possible hypersensitiveness of the tissues was necessary for arthritis to develop. He was unable to determine the rôle played by allergy. In the hypertrophic type no definite evidence of infection had been found. The most probable causes were endarteritis of the small blood vessels and trauma in persons who were overweight and who showed senile changes in the tissues. Heredity seemed to play a definite rôle in hypertrophic arthritis. A review of the bacteriologic investigation in arthritis was given.

Fletcher²⁷ found that a liberal use of vitamins and a moderate restriction of carbohydrates were valuable measures in the treatment for arthritis, particularly when roentgenograms showed functional abnormalities in the enteric tract. After the feeding of vitamin B in large amounts, he noticed improvement in tone in the large bowel and a reappearance of the haustral markings. Large quantities of carbohydrate seem to favor the development of deficiency diseases.

Crowe,²⁸ reiterating his belief that all cases of arthritis were due primarily to bacterial infection, discussed his method of treatment with vaccine. This consisted in giving the smallest possible dose that stimulated the tissue cells. He believed that a local reaction should be avoided if possible, and that a general reaction should never be produced. The criterion of an effective dosage was a decrease in the swelling, pain and stiffness of the joints. Stock vaccines, including a number of varieties of nonhemolytic streptococci and *Micrococcus deformans*, were used as a rule, and had been found to be as effective in most cases as autogenous vaccines.

Ely²⁹ observed that the same pathologic lesions in the joint might be produced by many different conditions. Atrophic, or type 1, arthritis he believed to be due entirely to bacteria. In many patients with this variety of arthritis the lesions of the joints healed when the supply of bacteria was shut off by the removal of foci of infection, in others, the bacteria were capable of maintaining an independent existence in the joints. The cause of hypertrophic, or type 3, arthritis remained unknown. The disease might originate from the presence of living organisms, presumably protozoan, in the bone near the joint. These organisms were normally considered harmless when found in the intestinal tract. They might gain entrance at the root of a dead tooth. In such cases extraction of dead teeth and administration of parasitocides were indicated. In most cases of arthritis the ruthless removal of so-called foci of infection was unnecessary, unscientific and often harmful.

27 Fletcher, A. A. J. Lab. & Clin. Med. **15** 1140, 1930.

28 Crowe, H. W. J. Lab. & Clin. Med. **15** 1072, 1930.

29 Ely, L. W. J. Lab. & Clin. Med. **15** 1264, 1930.

Allergic Arthritis—Freiburg and Dorst³⁰ found what they called the allergic type of joint in more than 30 per cent of 100 cases of arthritis. The clinical picture was that of a fusiform swelling with slight or no periarticular infiltration. There was moderate limitation of motion, the capsule of the joint was distended with fluid and "boggy" to palpation. Pain was usually slight. The patients sought treatment because of the stiffness or swelling. The fluid in the joint was clear and straw-colored, and contained a few cells, chiefly lymphocytes or large mononuclears. Cultures obtained from the fluid were negative. The physical properties of the fluid suggested a transudate rather than an exudate. Cultures were made of organisms obtained from the nose, sinuses, throat and enteric tract. Hypersensitiveness to these organisms was then tested by cutaneous reactions. A vaccine was made of the organisms giving positive cutaneous reactions. This vaccine was given in very small doses, the initial dose usually being 0.5 minim (0.03 Gm.)

Dietetics—Snyder and Traeger³¹ concluded from their clinical observations that proper dietary instruction was an important part of the therapy in arthritis. The patients were first placed on a basic diet, and this was regulated later in regard to the general condition, weight, clinical composition of the blood and clinical progress of the patient. This basic diet had the following characteristics: a low caloric value, a low carbohydrate value, an adequate vitamin content, elasticity and availability.

Results of Sympathetic Ganglionectomy—Hench, Henderson, Rowntree and Adson³² concluded from their observations of sympathetic ganglionectomy and trunk resection in 30 cases of chronic arthritis that these procedures had a limited application. As suitable for operation they selected patients with atrophic arthritis in whom the disease was chiefly periarticular, with little bony alteration except atrophy. Improvement after operation could be expected only in those cases in which definite peripheral vascular changes resulted when the sympathetic control was temporarily removed. This was tested by giving a large dose of typhoid vaccine. No patient was operated on who was over 45 years of age. In all the patients the disease was progressively getting worse but was mainly confined to the extremities. All of the patients were given general treatment for from six to twelve months before operation was considered. The effects of the operation were a marked vasodilatation, with an increased flow of blood in the capillaries, an

30 Freiburg, J. A., and Dorst, S. E. J. Lab. & Clin. Med. **15** 1109, 1930

31 Snyder, R. G., and Traeger, C. H. J. Lab. & Clin. Med. **15** 1214, 1930

32 Hench, P. S., Henderson, M. S., Rowntree, L. G., and Adson, A. W. J. Lab. & Clin. Med. **15** 1247, 1930

increased surface temperature in the extremities, the abolition of reflex sweating, loss of the pilomotor reflex, a positive Horner's syndrome and slight atrophy of the muscles of the shoulders. The relief from pain varied from complete relief to no change. The authors were unable to offer a satisfactory explanation for the relief from pain, and they felt that at the present time no definite statement could be made with regard to the value of these operative procedures in arthritis.

Gonorrheal Arthritis—Kinsella³³ expressed the belief that allergy played a rôle in gonorrheal arthritis. The arthritis never appeared with acute urethritis, but usually followed an intercurrent infection or intoxication later. This suggested the development of a state of hypersensitiveness before symptoms appeared in the joints. The author recognized two types of gonorrheal arthritis: (1) a simple effusion into the joint, cured by aspiration and splinting, and (2) an extra-articular induration. For the second type incision and drainage of the most congested and tender areas were advised, followed by early motion in the joint.

Spinal Types of Arthritis—In 80 unselected persons over 40 years of age, Cottrell³⁴ found osteoarthritis of the spine by roentgenography in 44 per cent. The average age of the patients was 55.6 years, and the dorsolumbar region was the part most frequently involved. Thirty-one per cent showed evidence of pressure on the spinal nerve roots. In 17 cases (21 per cent) there were no arthritic symptoms. Eight patients (10 per cent) had the radicular syndrome, and of these, 5 had been operated on for supposed abdominal conditions without relief.

At a medicolegal conference, Putti³⁵ discussed the types of arthritis of the spine, classifying the two common types as spondylitis deformans and ankylosing spondylarthritis and calling attention to a third form of vertebral arthritis that involved the posterior articulations. The last type was shown infrequently and with difficulty by roentgenography. He believed that in cases of arthritis, trauma that seemed trivial might cause symptoms to develop in joints that had been "silent" previously, and that these symptoms might persist for long periods and disable the patients. Such arthritides were the cause of many disabilities in laborers. On the other hand, congenital anomalies rarely were important factors in causing persistent disabilities.

Sedimentation Tests—Dawson, Sia and Boots³⁶ performed 500 sedimentation tests on 220 patients suffering from arthritis. They found

33 Kinsella, R. A. *J. Lab. & Clin. Med.* **15**: 1062, 1930.

34 Cottrell, J. C. *Surg. Gynec. Obst.* **51**: 731, 1930.

35 Putti, V. *Riforma med.* **46**: 999, 1930.

36 Dawson, M. H., Sia, R. H. P., and Boots, R. H. *J. Lab. & Clin. Med.* **15**: 1065, 1930.

that the sedimentation rate was moderately or markedly increased in practically all cases of active atrophic arthritis. There was a fairly close relationship between the rate of sedimentation and the severity and extent of the arthritis. An increased sedimentation rate was commonly observed with exacerbations of the disease and a decreased rate with remissions. The sedimentation reaction tended to return to normal in cases that became arrested. In hypertrophic arthritis a slight increased sedimentation rate was usually found. Cases of myositis, fibrositis and neuritis showed the least variation from the normal (usually a very slight increase) in the sedimentation reaction.

Rheumatoid Nodules—Dawson and Boots³⁷ studied the subcutaneous nodules found in rheumatoid (chronic infectious) arthritis. Bacteriologic investigations of these nodules gave entirely negative results. With the exception of those peculiar to rheumatic fever, similar nodules were not observed in any other disease. There was a striking resemblance between the subcutaneous nodules occurring in rheumatic fever and those observed in rheumatoid arthritis. This resemblance suggested the possibility that these two clinical entities might be different manifestations of the same fundamental pathologic process.

[ED NOTE—We are unable to draw any definite conclusions from these articles in respect to the causation of chronic arthritis. Evidently a number of factors play a part, even though microorganisms seem responsible for most of the actual changes in the joints. From the standpoint of treatment as much or more may be accomplished by efforts to render the soil less favorable than by attention directed only to the eradication of the seed. We regard it as distinctly encouraging and offering hope for the future that arthritis has come to occupy so prominent a position as a subject for study that such an excellent variety and quality of articles as those mentioned, dealing with various phases of the problem, should appear within a short period.]

VASCULAR DISTURBANCES OF THE EXTREMITIES

Smithwick and White³⁸ treated 11 patients with vascular disease of the lower extremity by injections of alcohol into the sensory nerves. This method permitted the painless dressing of gangrenous areas, infection could be more easily controlled and exercises could be done more easily to improve the circulation. It was felt that amputations were avoided by this means in 6 of the 11 cases. As a result of these alcoholic injections, sensation in the area supplied by the nerve was usually lost for from three to six months.

37 Dawson, M. H., and Boots, R. H. Subcutaneous Nodules in Rheumatoid (Chronic Infectious) Arthritis, *J. A. M. A.* 95:1894 (Dec. 20) 1930.

38 Smithwick, R. H., and White, J. C. *Surg. Gynec. Obst.* 51:394, 1930.

Morton and Scott³⁹ used spinal anesthesia, as employed in various operative procedures, to determine sympathetic vasoconstrictor activity in the lower extremities. In persons without vascular disease there was a fairly constant temperature for each part, showing a slightly varying but progressive rise in temperature (measured with a thermocouple) from knees to toes. After the injection of a spinal anesthetic the entire surface of the skin of the lower part of the leg attained approximately the same temperature. In vascular disabilities of a vasospastic nature the cutaneous surface of the lower part of the leg reached approximately the same temperature as in normal persons. When there was disease of the vessels or mechanical obstruction, no rise or only a slight rise was noticed after spinal anesthesia.

Posttraumatic Painful Osteoporosis—Leriche and Fontaine⁴⁰ discussed the subject of painful posttraumatic osteoporosis. Following a peripheral traumatism, apparently not severe, there occurred stiffness, pain on use, atrophy and edema. Little importance was attached to these symptoms if the roentgenogram made after the accident showed the bones intact. Physical therapy was usually employed, often with aggravation of the situation. The symptoms became more severe, and after two or three months roentgenograms showed rarefaction of the epiphyses with the appearance of small cavities suggestive of tuberculosis. A plaster cast was applied, pain continued, and the cast was changed without improvement. After about six months the pain subsided, but the joint remained stiff. Finally, in ten or twelve months "healing" was complete, often with partial, but sometimes with total ankylosis.

This was the clinical picture of traumatic osteoporosis, but surprising transformations might result from sympathectomy. After sympathectomy (more often periaxial) one saw the rarefied bone reform both as to texture and outline and in a few weeks regain a normal roentgenologic appearance. Limitation of motion, pain and weakness disappeared. In a few hours the patient was better, and in a few days had the impression that he was cured. These facts were inexplicable. One might consider it as a law that active hyperemia created a rarefaction of bone, and that there was no rarefaction without hyperemia. It was paradoxical that sympathectomy which also produced hyperemia should have a beneficial therapeutic effect on this condition. The authors only presented the facts, the explanation was to be found later. It was probable that in conditions of hyperemia there were a variety of physiologic states that had not been completely differentiated. On the other hand, traumatic osteoporosis was not of purely vasomotor origin. The

39 Morton, J. J., and Scott, W. J. M. *J. Clin. Investigation* 9: 235, 1930.

40 Leriche, R., and Fontaine, R. *Presse med.* 38: 617, 1930.

authors had treated 16 patients for this condition with periarthral sympathectomy. The pain had disappeared the same or the next day, and the patients had been able to effect movements which previously were impossible. The relief had been permanent.

[ED NOTE—This observation is important for three reasons; (1) The aforementioned paradox was noted, (2) an effective method of treatment seems to have been found, (3) a suitable name for a fairly frequent condition has been supplied. If rarefaction of bone results only from hyperemia, we should like to know how the authors explain atrophy of the bone following immobilization of an extremity.]

DISEASES OF THE NERVOUS SYSTEM

Sympathectomy in Spastic Paralysis—In 1927, Royle on his visit to England performed ramisection on 6 patients selected by himself as likely to be benefited. These patients were seen prior to operation and were observed afterward by Symonds,⁴¹ a neurologist, and by a group of six orthopedic surgeons whose conclusions in 1930 were: 1. The operation of cervical or lumbar ramisection is without effect on the rigidity due to extrapyramidal disease. 2. The rigidity of pyramidal disease, as seen in conditions of hemiplegia and quadriplegia in children, might be temporarily diminished after the operation. This temporary diminution of tone had been observed in both upper and lower limbs with some improvement of voluntary power. The diminution of tone and the improvement in function were, however, short-lived, within a few weeks or months, notwithstanding continuous measures of reeducation under experienced medical supervision, the condition of the patients remained as before the operation. In the opinion of several surgeons who examined these patients both before and shortly after the operation, the diminution of tone was no more than might be seen after any major surgical procedure with postoperative shock.

On the other hand, Wade⁴² as a result of reviewing 38 cases concluded that the operation of ramisection with tenotomy and reeducation should be the procedure of choice in cases of spastic paralysis.

At the meeting of the British Medical Association at Winnipeg in 1930, Royle⁴³ reaffirmed his faith in his operation for the treatment for spastic paralysis, claiming that 70 per cent of his patients so treated had been benefited.

At the same meeting, Fulton⁴⁴ in discussing the mechanism of postural responses pointed out that the stretch reflex, which is at the

41 Symonds, C. P. *Lancet* 2 127 (July 19) 1930.

42 Wade, R. B. *J. Coll. Surgeons, Australasia* 2 406 (March) 1930.

43 Royle, N. D. *Lancet* 2 639 (Sept 20) 1930.

44 Fulton, I. F. *Lancet* 2 645 (Sept 20) 1930.

basis of posture, was abolished by division of either the posterior or the anterior roots but not by sympathectomy, although the transient diminution in rigidity occurring in spastic paralyses after ramisection suggested that the operation might cause an increase in the threshold for eliciting the stretch reflex. Fulton thought that apart from certain visceral conditions, such as Hirschsprung's disease, the only clearcut indication for sympathectomy was ischemia, and that any pathologic process in which healing would be greatly accelerated by an increased supply of blood offered an indication for ramisection.

(To be continued)

PNEUMATIC RUPTURE OF THE INTESTINAL CANAL

WITH EXPERIMENTAL DATA SHOWING THE MECHANISM OF
PERFORATION AND THE PRESSURE REQUIRED *

CON AMORE V BURT, M D

BROOKLYN

Pneumatic rupture of the intestinal canal is one of the most uncommon conditions, and is due to the introduction of air under pressure into the oral cavity or the rectum

Forty cases of pneumatic rupture of the alimentary canal, including one case of rupture of the esophagus, have been reported previously. The one reported and the three referred to in this paper increase the total to forty-four cases.

Twenty-six years ago (1904), G W Stone¹ of London reported the first case of pneumatic rupture of the intestine. The other cases recorded are Andrews,² one, with a review of fifteen others, Bendixen and Blything,³ one, with a collection of seven others, Fauquez⁴ and Jean⁵ of France, two each, and one each by Block and Weissman,⁶ Buchbinder,⁷ Cotton,⁸ Duval⁹ of France, Hailes¹⁰ of Australia, Hays,¹¹

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* From the First Surgical Service, Methodist Episcopal Hospital

1 Stone, G W Rupture of Bowel Caused by Compressed Air, *Lancet* 2 216, 1904

2 Andrews, E Wyllys Pneumatic Rupture of the Intestine A New Type of Industrial Accident, *Surg Gynec Obst* 12 63, 1911

3 Bendixen and Blything Pneumatic Rupture of the Bowel, *Surg Gynec Obst* 18 73, 1914

4 Fauquez Bulletin chirurgical des accidents de travail, 1925

5 Jean, G Ruptures recto-coliques produites par l'air comprime (reported with C Lenormant), *Bull et mem Soc de chir de Paris* 47 440, 1921, Ruptures recto-coliques produites par l'air comprime, *Presse med* 29 675, 1921, abstr, *J A M A* 77 1137 (Oct 1) 1921 Lenormant, C Une variete d'accident du travail, Les ruptures du tube digestif produites par l'air comprime, *Presse med* 19 486, 1911

6 Block, F B, and Weissman, M I Pneumatic Rupture of the Sigmoid Report of a Case, *J A M A* 86 1597 (May 22) 1926

7 Buchbinder J R Pneumatic Rupture of the Intestine, *J A M A* 76 518 (Feb 19) 1921

8 Cotton, F I Rupture of the Bowel from Compressed Air, *Boston M & S J* 166 562, 1912

9 Duval, P Bull et mem Soc de chir de Paris 47 450 1921

10 Hailes, W A Rupture of Bowel by Compressed Air, *M J Australia* 2 538, 1921

11 Hays, G L Pneumatic Rupture of the Bowel, *Surg Gynec Obst* 43 491, 1926

Houzel¹² of France, Morris,¹³ Schwartz¹⁴ and Sparkman¹⁵ Petrin¹⁶ of Germany presented one case of rupture of the esophagus

THE PRESSURE REQUIRED TO RUPTURE THE VARIOUS PARTS OF THE INTESTINAL TRACT

An extensive search of the original literature reveals that very little work has been done on this subject, and that few details have been presented by the investigators who have published their results. No detailed or systematic study of the pressure required to rupture the various portions of the alimentary tract has been recorded. No attempt has been made to demonstrate the mechanism of rupture, and there is presented no comparison of the relative strength of the various sections.

E. Quenu¹⁷ of France was the first investigator to publish the results of an experiment along these lines. In 1882, in the *Revue de Chirurgie*, he described the technic for this procedure. He dissected the anus free and ligated its lower portion. Then by the use of a pressure pump he introduced air into the upper portion of the rectum, and found that the intestines would bear a pressure of from 50 to 60 cm of mercury without rupturing. At a pressure of 70 cm of mercury the peritoneum ruptured in several places, this was followed immediately by the rupture of the other coats. He stated that it is not reasonable to suppose that the same pressure is required to rupture the intestine within the body.

In 1911, E. Wyllys Andrews² of Chicago published the only other data that I have found relative to this subject. Using a pressure gage and a tank of compressed air, he did some experiments on the pressure required to rupture human, dog and ox intestines outside the body. He found this to be from 6 to 10 pounds (2.7 to 4.5 Kg). Andrews further tested fresh specimens of the stomach, bladder and intestines from meat shops and from experiments on the dog, and never found one capable of bearing more than 12½ pounds (5.6 Kg), most of them rupturing with a pressure of between 7 and 8 pounds (3.2 and 3.6 Kg). He stated that Senn found that a bowel diseased with enteritis ruptured at 1½ pounds (0.7 Kg) of pressure.

12 Houzel, G. Rupture of Intestine by Compressed Air, *Arch med-chir de Province* **16** 513, 1926.

13 Morris, R. B. Pneumatic Rupture of Intestine with Roentgen Ray Studies Following Recovery. Case Report, *Am J Roentgenol* **18** 560, 1927.

14 Schwartz, H. Pneumatic Rupture of the Intestine, *J A M A* **78** 1802 (June 10) 1922.

15 Sparkman, J. R. Unusual Case of Intestinal Rupture, *J South Carolina M A* **18** 324, 1922.

16 Petrin, G. Ein fall von traumatischer Oesophagusruptur, nebst bemerkungen uber die Entstehung der Oesophagusrupturen, *Beitr z klin Chir* **61** 265, 1908.

17 Quenu, E. Des ruptures spontanees du rectum, *Rev de chir*, 1882, p 173.

In 1921, P. Duval of France stated that he believed the dominant factor in the perforation of the intestine to be the rapidity of introduction of the air rather than the degree of pressure used. He cited one case with enormous abdominal dilatation which was shown by roentgen ray to be due to gaseous distention of the large intestine. This patient was said to present a picture typical of a total megacolon, and under this diagnosis went to the operating room, where a laparotomy showed neither a lesion nor a malformation of the colon. On further questioning of the patient after the operation, Duval learned that the patient had inflated his colon by forcing air through the anus with a bicycle pump. The pressure was not sufficiently elevated to cause a rupture of the intestine, probably because the introduction of the pressure was under the control of the patient.

In view of the marked incompleteness of information relative to the pressure required to rupture the intestines, I became interested in this problem, and performed numerous experiments on the human intestine in the autopsy room. Portions of the rectum, sigmoid, transverse colon, cecum, ileum, jejunum, stomach and esophagus have been selected. When possible the mesentery was removed with the specimens.

EQUIPMENT EMPLOYED

The equipment (fig. 1) employed for the measurement of the pressure was a manometer which I devised. It consists of a millimeter scale beside a "U" glass tube, 4 mm in internal diameter, containing mercury, supported by a wooden upright stand, and a tank of compressed air. The pressure of the air in the tank may be at any height so long as it is well above that at which rupture of the specimens occurs. The approximate maximum pressure in the tanks used for this experimentation was 65 pounds (29.5 Kg.) per square inch. The release apparatus was made so as to permit either a rapid or a slow exit of the confined air. To the manometer and to the tank was attached, by means of pressure rubber tubing, a curved glass tube (Paul's) so constructed that there was an elevated ridge near the end of the tube, which prevented the specimen from slipping off when it was securely fastened and pressure applied. A valve of an automobile tire was placed in the tube leading from the tank to the specimen for the purpose of maintaining the pressure in the specimen at any particular point, so that observations could be made.

APPLICATION AND RECORDING OF PRESSURE

The specimens from 5 to 6 inches (12.5 to 15 cm.) in length were attached by means of 2 inch (5 cm.) gauze bandage tied securely around the ends of the segments of the intestine which had been slipped over the free ends of the glass tubes as shown in figure 1 where a portion of

transverse colon was attached to the equipment. Inflation was begun by releasing compressed air at the rate of about 2 cm (0.38 pounds) of mercury per second. The reading of the manometer was recorded when the first rupture occurred and again when perforation of the mucosa took place, or when a simultaneous rupture of all of the layers occurred. On the manometer the reading from the starting point of the column of mercury to the point of rupture was multiplied by two in

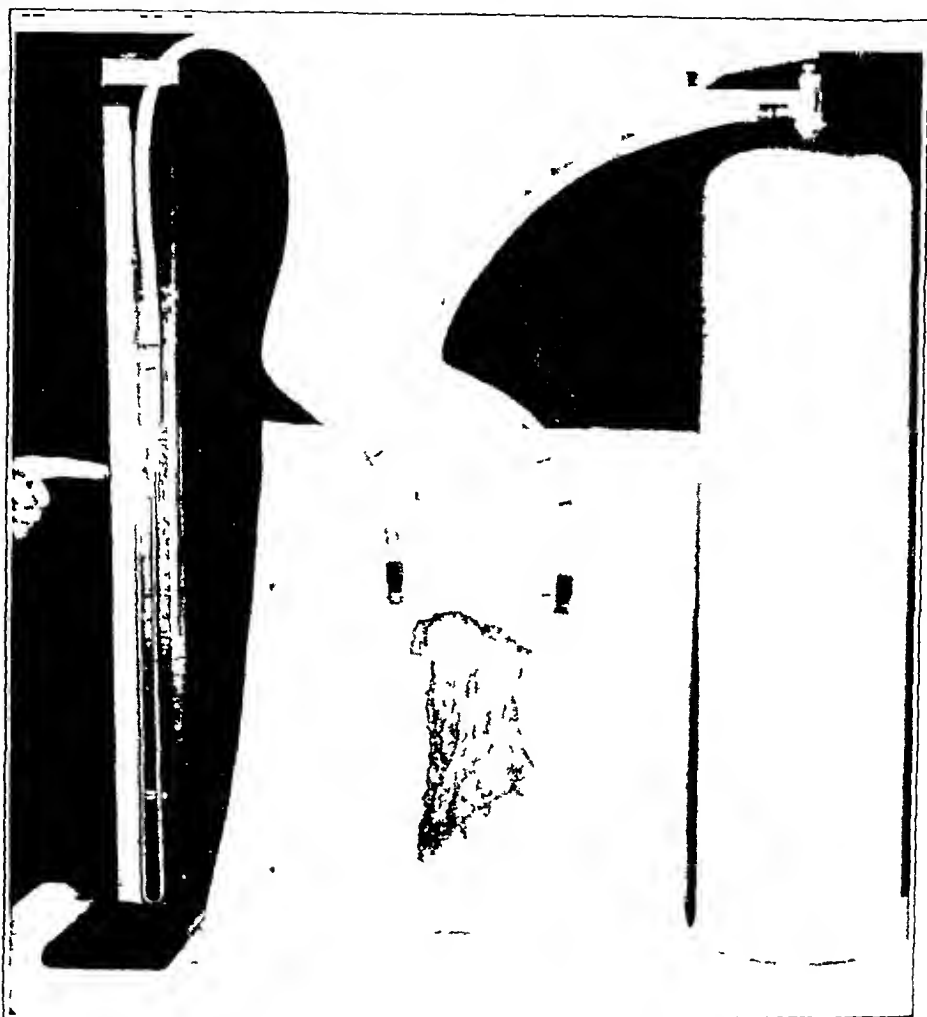


Fig 1—Equipment used in measuring the pressure required to rupture the intestines. The mercury manometer and tank of compressed air are connected by rubber tubes with attached Paul's tubes, and a section of transverse colon, partially inflated. The hand points to the level of the mercury in the manometer. The black line in the tube leading from the tank is where the tire valve is located.

order to obtain the pressure in centimeters of mercury at which the perforations took place. For convenience and uniformity of expression of results by observers it was necessary to convert the manometer readings into pounds per square inch. At 20 C (average room temperature) 1 cm of mercury is equivalent to 0.1915 pound per square inch.

When the pressure in centimeters of mercury at which the ruptures took place was multiplied by 0.1915, the pressure in pounds per square inch was obtained. These are recorded in table 1 for each specimen tested.

DATA AND THEIR COLLECTION

Data are presented in table 1 from observations on eighty-seven specimens following autopsies on seven females and eleven males, ranging in age from 5½ months to 82 years, with an average age of 42.1 years. This series includes one male child of 5½ months, one female child of 8 months and a male child of 11 years. The cause of death in each instance, the age of the patient and the particular specimens used are recorded. It will be observed that the points of rupture are not presented for many of the specimens, which is due to the fact that they were either unsuitable for testing or were discarded when the rupture did not occur entirely free from the point of attachment to the pressure equipment, thus eliminating the possibility of tearing as a result of the application of the ligature.

GENERAL OBSERVATIONS

It may be generalized from table 1 that the average pressure required to rupture the outer two coats of the various portions of the intestinal canal was 3.49 pounds per square inch and that required to perforate the wall was 4.07 pounds per square inch. In children below 12 years of age a somewhat higher pressure was required than in the specimens from older persons. The rectum supported the greatest average pressure, and the sigmoid, ileum, esophagus, jejunum, transverse colon, cecum and stomach are in order in point of decreasing pressure required to rupture these specimens. No section was found to support a greater pressure than 11.59 pounds per square inch, which was borne by a segment of sigmoid from a child of 11 years. The greatest pressure supported by a specimen from an adult was 8.36 pounds per square inch, borne by a section of ileum.

ANATOMY

Before considering the mechanism of rupture a brief review of the anatomy of the various portions of the alimentary canal is presented. The entire tract consists of four layers, from within outward, the mucosa, the submucosa, the muscularis, which is composed of an inner circular and an outer longitudinal layer of smooth muscle, and the serosa except in the case of the esophagus in which the serosa is replaced by a fibrous layer which attaches the esophagus to the surround-

ing structures. The large intestine differs from the small intestine in that the outer longitudinal layer of the muscularis of the colon is chiefly collected into three longitudinal bands of smooth muscle, which extend throughout the length of the colon. These are shorter than the inner layers, and the intestine is shortened to accommodate them, resulting in the formation of the sacculations or haustra.

TABLE 1—*Observations on Sections from the Rectum, Sigmoid,*

Cause of Death	Sex	Age	Rectum		Sigmoid		Transverse Colon	
			Serosa	Mucosa	Serosa	Mucosa	Serosa	Mucosa
Toxic encephalitis	M	5½ mo	10 26 AM	12 35 AM	10 64 LBL	11 78 AM	6 08 LBT	6 84 M
Upper respiratory infection, bilateral antritis	F	8 mo			5 32 LBL	11 02 AM	4 84 LBL	6 87 AM
Sinus thrombosis, postoperative pneumonia	M	11 yr			10 07 LBL	11 59 AM		
Lobar pneumonia	F	21 yr	4 56 LBL	4 94 AM	5 32 LBL	6 08 AM	2 66 LBL	3 42 AM
Appendectomy and suspension of uterus, sudden death 12 hours after operation	F	30 yr			2 29 LBL	5 60 AM	1 52 LBL	4 09 M
Subacute bacterial endocarditis	M	30 yr			3 42 LBL	3 61 M	1 14 LBL	2 28 M
Subacute bacterial endocarditis (edema of intestines)	M	37 yr			2 66 LBT	3 04 AM		
Chronic nephritis	M	42 yr			3 80 LBT	4 56 M	1 90 LBL	2 85 AM
Pyonephritis with uremia	M	42 yr			2 66 LBL	2 66 M	1 90 LBL	3 04 AM
Gangrene of hand lymphangitis and lymphadenitis	M	43 yr			2 28 LBL	3 23 AM		
Intestinal influenza	F	45 yr	1 90 LBL	2 09 AM	2 66 LBL	2 66 AM	1 71 LBL	2 19 AM
Cirrhosis of liver, low grade peritonitis	F	50 yr			2 66 LBT	2 85 AM	1 52 LBT	1 71 AM
Chronic myocarditis with marked decompensation	F	60 yr			2 66 LBT	3 04 AM		
Chronic myocarditis with slight decompensation	F	60 yr			2 28 LBL	3 42 AM	0 76 LBL	1 52 AM
Arteriosclerosis with cerebral thrombosis	M	62 yr	3 04 LBL	3 42 AM	2 57 LBL	3 42 AM	1 90 LBL	2 28 AM
Bronchopneumonia	M	64 yr			4 75 LBJ	4 91 AM	1 52 LBL	2 09 AM
Arteriosclerosis, diabetes, chronic myocarditis	M	64 yr			1 14 LBL	2 95 AM	1 52 LBL	2 66 AM
Carcinoma of sigmoid, resection, local peritonitis	M	78 yr	3 80 LBL	3 80 M	2 28 LBL	3 42 M	2 28 LBL	2 85 AM
	M	82 yr						
Average pressure required to rupture the various specimens in pounds per square inch			4 71	5 32	3 86	4 99	2 20	3 06
Average pressure required to rupture the outer layers of the intestinal canal is 3 49 pounds per square inch								
Average pressure required to perforate the various sections of the intestinal canal is 4 07 pounds per square inch								

* The figures give the pressure in pounds per square inch at which the ruptures took place in the serosa (S), transversely (T) or longitudinally (L), and whether or not it took place on the mesenteric (M) or anterior (A) or posterior (P) surface of the stomach. In a few of the columns the second line

MECHANISM OF RUPTURE

Large Intestine—Gross Appearance. In the colon the ruptures took place in almost all of the specimens along one or more of the longitudinal bands at one or more points on the antimesenteric surface. The occurrence of the first rupture was generally in a longitudinal direction, though in many instances it was transversely across the muscular bands, and it involved the serosa and the muscularis. The rupture then extended along one or more of the longitudinal bands, and as the pressure was increased in the lumen of the segment, the serosa and

muscularis stripped back rapidly until a large part of the mucosa in the majority of cases was herniated through the opening in the outer two coats (fig 2) In many instances almost all of the serosa and muscularis stripped back markedly, and the mucosa was extensively ballooned out on the antimesenteric surface As the pressure was further increased, the herniated mucous layer perforated suddenly with a sharp,

*Transverse Colon, Cecum, Ileum, Jejunum, Stomach and Esophagus**

Cecum		Ileum		Jejunum		Stomach		Esophagus	
Serosa	Mucosa	Serosa	Mucosa	Serosa	Mucosa	Serosa	Mucosa	Fibrosa	Mucosa
3 23 LBT	5 89 AM	8 74 AM	9 50 AM	7 03 M	7 03 M	3 61 LC	3 61 LC	11 02 L	11 02 L
3 04 LBL	7 22 AM								
1 14 LBL	2 66 AM	4 94 AM 8 36 M	7 60 M 8 36 M	4 75 M 4 18 M	4 75 M 4 18 M	1 90 LAS 2 09 LC	1 90 LAS 2 09 LC	8 17 L 4 56 L	8 17 L 4 56 L
0 76 LBL	0 95 AM	3 42 AM 1 52 AM 2 66 AM	3 80 AM 3 42 AM 2 66 AM			1 14 APL	2 28 LC	4 47 L	4 47 L
1 09 LBT	1 90 AM	3 42 AM	3 42 AM					4 94 L	4 94 L
2 09 LBL	2 85 AM	2 66 M 3 04 AM	2 66 M 6 08 AM					2 66 L 3 23 L	2 66 L 3 23 L
1 52 LBL	2 28 AM	5 32 M 5 32 AM	5 32 M 5 51 AM						
		4 37 M	4 94 M						
1 52 I PL	1 90 AM	5 32 AM	5 32 AM						
0 76 LBL	1 52 AM					0 38 ASGC	0 76 LC	2 42 L	2 85 L
1 14 LBL	1 90 AM	4 56 M	4 56 M	3 80 M	3 80 M			3 80 L	3 80 L
1 14 LBL	1 14 AM	3 04 M	3 04 M						
0 95 I PL	1 14 AM	4 75 AM	4 75 AM	3 42 M	3 42 M			2 28 L	3 42 L
		3 04 AM	3 04 AM						
1 53	2 61	4 08	4 94	4 63	4 63	1 82	2 13	4 76	4 91

and muscularis and in the mucosa The abbreviations indicate whether the rupture occurred along the longit-
 erie (M) or the antimesenteric (AM) surface, or on the lesser or greater curvature (LC or GC) or on the
 of figures gives the pressure at which the specimens ruptured in situ

popping sound similar to that of the bursting of a toy balloon, leaving an extensive laceration of the outer two coats and a small, ragged mucosal perforation, or the remaining tissue gradually thinned out into a fine mesh and became so thin that the air escaped through it slowly No specimen showed more than one perforation in the mucosa

Occasionally a rupture occurred on the mesenteric surface after the outer two coats had stripped back and left a large part of the mucosa herniated In the mesenteric ruptures the air dissected up the serosa for a considerable distance along the intestinal wall and around its circumference and finally caused rupture at one or more fine points

either in the mesentery proper or more commonly along the sides of the colon

In no instance did the perforation occur on the mesenteric surface until there had been an antimesenteric rupture of the outer two coats, with herniation of the mucosa. In many instances the muscularis ruptured in several places throughout the specimen before either the mucosa or the serosa ruptured, as may be seen by the irregular distribution of these small masses of muscle between the intact inner and outer layers of the intestinal wall.

Microscopic Appearance In order to demonstrate as nearly as possible the mechanism of rupture of the alimentary tract in the majority of cases, I have selected four microscopic sections prepared from a specimen of ascending colon ruptured at 10.53 pounds per square inch from a man of 60. It will be noted that as the pressure was applied in the specimen there was first a rupture of the serosa with slight

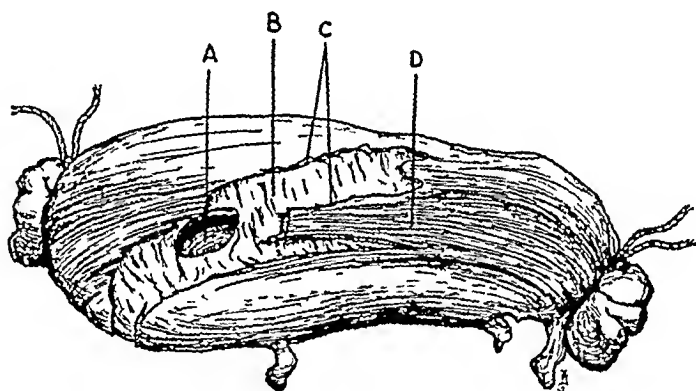


Fig 2—A section of colon, showing a perforation (A) in the mucosa (B), which is herniated through a laceration in the serosa and muscularis (C). The laceration extends principally along the longitudinal band (D).

separation of the underlying external muscular layer (fig 3). The outer muscular layer was then completely lacerated, and there was a slight tear in the inner muscularis with a general separation of all of the layers (fig 4). With further increase in pressure, the serosa stripped back, the muscular layers separated and frayed out, the submucosa was lacerated and only the mucosa remained intact. There was a tendency to curling or rounding of the lacerated ends of the two muscular layers with the outer of these two curling over the torn ends of the inner circular fibers indicating the tension under which the rupture took place and the tendency toward retraction of these ruptured layers. There was a noticeable appearance of general laceration and separation of all of the layers (fig 5). A section of the edge of the perforation showed that the serosa had disappeared, the muscular layers had both retracted, and the mucosa and submucosa presented a marked wrinkling

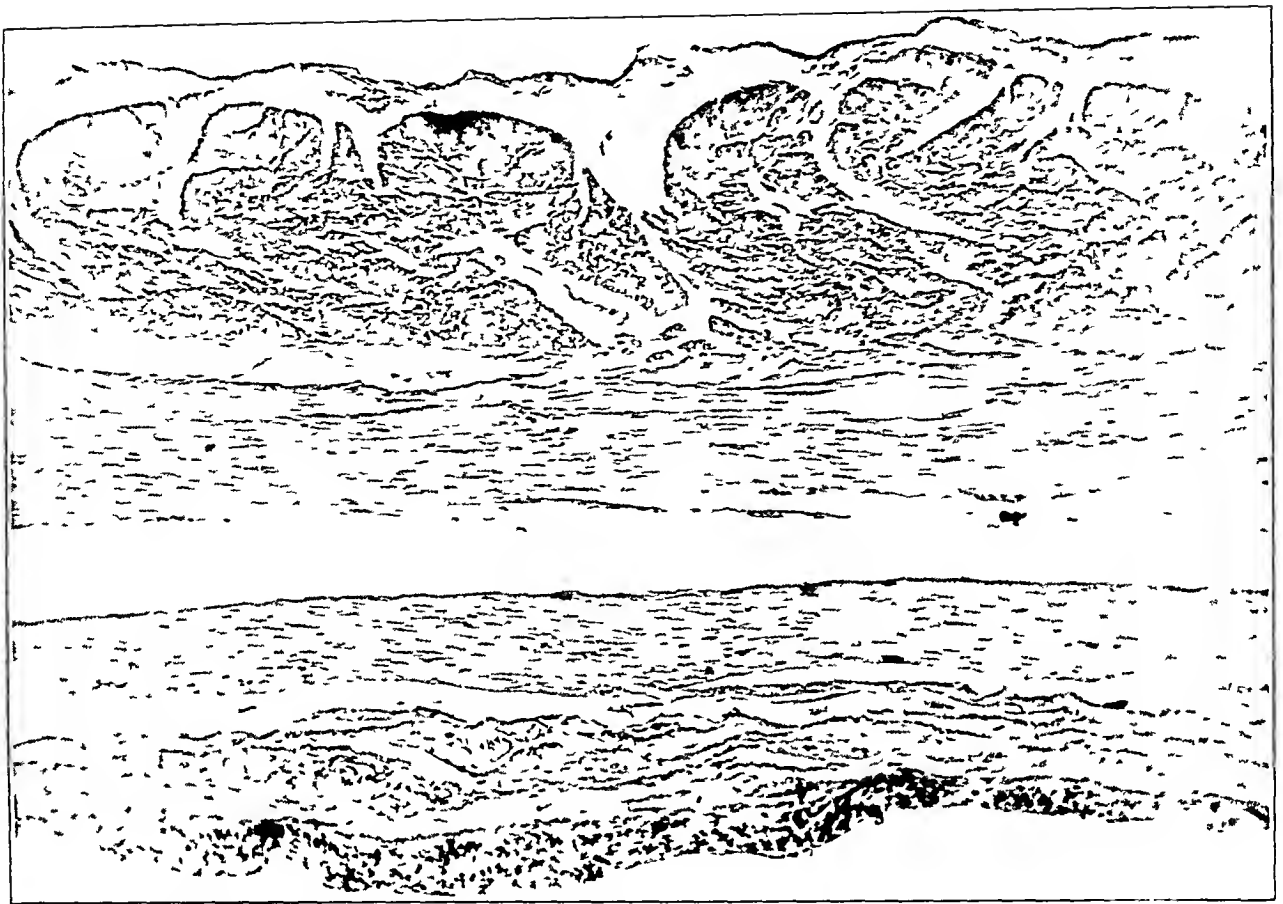


Fig 3—Photomicrograph of the ascending colon, showing rupture of the serosa with slight underlying laceration of the outer longitudinal muscular layer. Otherwise the section presents normal relations.

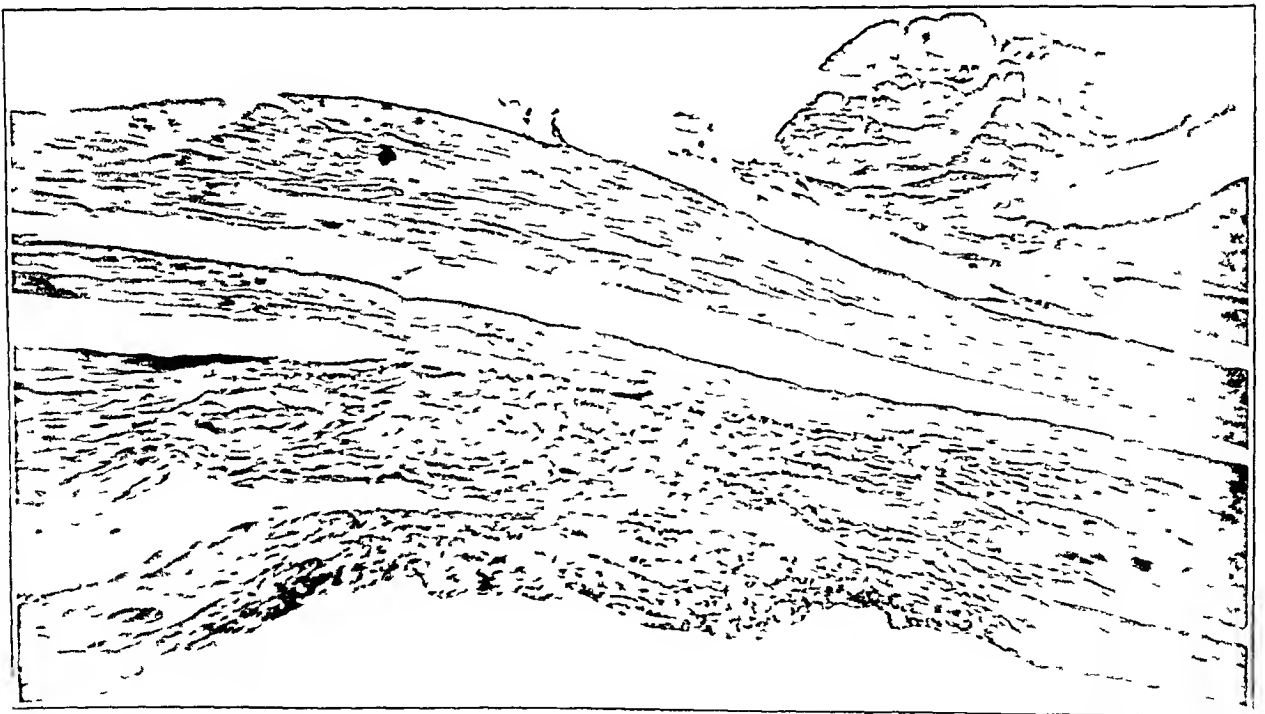


Fig 4—Photomicrograph of the ascending colon. Note the absence of the serosa, the complete transverse separation of the outer longitudinal muscular layer and an incomplete laceration of the inner circular muscularis.

following the rebound after the enormous distention and perforation (fig 6)

In the meshlike lacerations and perforations of the colon, the muscular layers were markedly torn and separated, and the fibers were aggregated irregularly in small bits over the stretched mucosa. On perforation, the mucosa lost its continuity and retracted considerably, while the submucosal and subserosal connective tissue formed the larger portion of the mesh.



Fig 5—Photomicrograph of the ascending colon, presenting an absent serosa, a completely severed and frayed out muscularis, a lacerated submucosa and an intact mucosa. Note the tendency to curling of the torn ends of the muscularis, and the appearance of general laceration and separation of all of the layers.

As the mucosa was the last of the layers to rupture, in view of its greater elasticity, it would seem that it should retract more than the others, which was shown in all of the specimens after complete perforation, particularly demonstrated in figure 6.

In the specimens showing grossly a mesenteric rupture, the mesenteric and subserosal tissues showed numerous small air pockets with a dissection of the serosa from its underlying structures.

Small Intestine—Gross Appearance In slightly more than half of the specimens of the small intestine the ruptures took place about the middle of the antimesenteric surface. Generally all of the layers ruptured simultaneously with much the same popping sound as in the perforation of the mucosa of the colon leaving a small, ragged perforation of from 0.5 to 2 cm. in diameter, involving all of the layers to about the same extent. The serosa and muscularis separated and



Fig 6—Photomicrograph of the ascending colon, showing the edge of the perforation. The mucosa and submucosa are markedly wrinkled following retraction after the enormous distention. The muscularis has separated and retracted considerably and the serosa is absent.

stripped back very little compared with the colon. In only two instances were lacerations noted in the outer two coats extending throughout most of the length of the specimens in contrast to the usual lacerations throughout the entire length of the sections of the colon. Transversely the edges were separated relatively slightly and thus allowed only a small

degree of herniation of the mucosa prior to the perforation (fig 7) In the remainder of the specimens there occurred mesenteric perforations (usually from 1 to 3 cm in diameter) in the mucosa, without any previous antimesenteric lacerations of the outer two coats Through the perforation in the inner coat, the air escaped into the subserosal spaces and dissected up the serosa both longitudinally and circumferentially for a considerable distance, involving about one half of the circumference of the specimen, and finally ruptured through at one or more very minute points in the serosa It was impossible to locate the points of rupture without immersing the specimens in water

Microscopic Appearance The small intestine (reports on sections are not included in this paper because of their similarity to the sections of the colon) showed essentially the same mechanism of rupture as was demonstrated in the large intestine There was, however, a tendency toward less general laceration and separation of the tissues, and for all of the layers of the small intestine to rupture simultaneously, as illus-

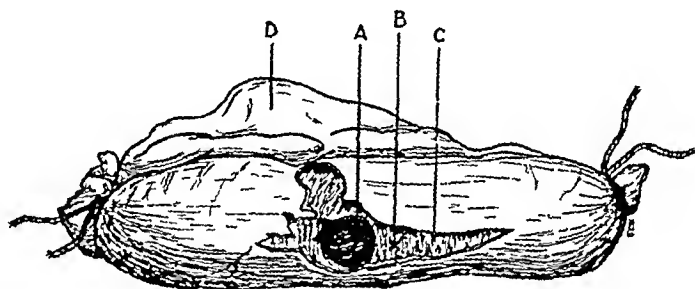


Fig 7—A section of ileum, presenting a perforation (A) in the mucosa (B), which is herniated slightly through a small laceration in the serosa and muscularis (C) The mesentery (D) is shown attached

trated in figure 8 This section was taken from a gross specimen selected primarily to demonstrate the intact mucosa with a laceration of the serosa and muscularis In addition to the typical laceration of the serosa and muscular layers, it exhibited a perforation of the mucosa just beyond the rupture of the outer two coats, thus confirming the tendency for all of the layers to rupture simultaneously

Esophagus—Gross Appearance In this organ there was first a separation of the muscular layers with a relatively slight herniation of the mucosa and a rupture of the mucosa throughout almost its entire length with a simultaneous meshlike rupture of the outer or fibrous coat usually in such a way as to release the pressure rather slowly Frequently, however, there was a complete perforation of all of the layers with the usual popping sound

Microscopic Appearance The thick muscular layers were separated and markedly retracted while the submucosa and perieso-

phageal tissue constituted most of the remaining wall, thus indicating the greater elasticity of the connective tissue

Stomach—The few specimens that were tested successfully were attached to the pressure equipment at the lower end of the esophagus and at the beginning of the duodenum. These showed such irregular results that it is impossible to give any definite mechanism of the rupture of this organ

GENERAL CONSIDERATIONS

A few specimens adjacent to the ones removed for external observations were tested *in situ* and the results indicate that there is little or no difference between the pressure required to rupture the intestine *in situ* and that required to perforate it when removed from the body. Certainly no difference would be expected in the portions in which the

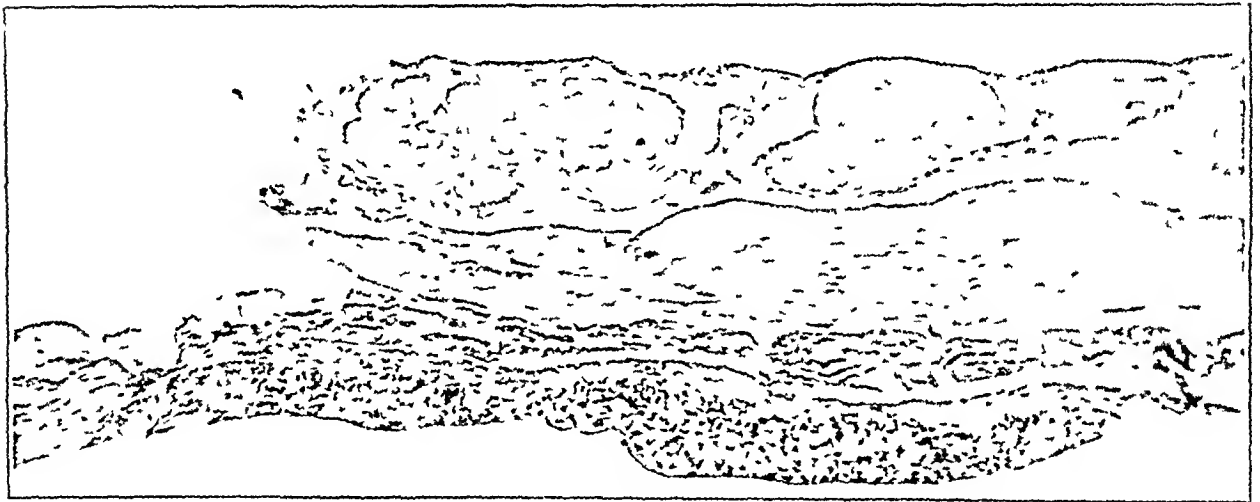


Fig 8—Photomicrograph of the ileum, taken primarily to show the laceration and separation of the serosa and muscularis with intact mucosa. It presents a complete laceration of the serosa and the muscularis down to the partially torn submucosa. Just to the right of the tear in the outer two layers is a perforation of the mucosa.

mesentery is long, and in which inflation would be the same inside and outside of the abdomen. There might be anticipated some difference in the cases in which the mesentery is short or absent, as in many cases of the ascending and descending colon and also in the duodenum but no appreciable difference has been observed experimentally (table 1).

In presenting these results, I am fully aware that the pressure used and the rapidity of its application in these experiments did not simulate exactly the conditions under which the patients mentioned in the literature were injured. It was necessary to apply the pressure relatively slowly in order to observe the sequence of events in the rupture of the specimens. It was thus possible to obtain accurate information as to the

mechanism of rupture I am also further aware that the data presented in table 1 are not sufficiently numerous to permit of conclusive observations, but they give a fair idea as to the pressure at which the various portions of the alimentary tract rupture and the manner in which the ruptures take place

The rapidity of the introduction of the pressure is probably more important than the actual pressure itself, for it is a common experience that, roughly, the same amount of pressure applied slowly to an object without destruction will, when applied quickly, demolish that object. For example, when one throws a fragile pasteboard box with considerable force, it goes forward rapidly, but if it is struck suddenly with the same force a hole is torn in it.

TABLE 2—*Comparison Between the Pressure at Which Perforation Took Place When the Air Was Introduced into the Intestinal Specimens Slowly and Then More Rapidly*

Sex	Age	Specimen	Perforation Shown in Pounds per Square Inch			
			With Slow Intro duction of Air		With Rapid Intro duction of Air	
			Number of Speci mens	Average Pressure at Rupture	Number of Speci mens	Average Pressure at Rupture
Male	5½ mo	Ileum	2	8.64	6	9.46
		Jejunum	1	7.03	3	7.28
Female	21 yr	Ileum	1	8.36	3	5.64
Male	21 yr	Ileum	1	6.46	1	6.27
		Sigmoid	1	5.61	1	3.80
Female	79 yr	Colon	2	2.80	5	3.32
		Ileum	2	7.22	12	5.68
		Jejunum	2	4.75	11	4.71
Average pressure at which perforation occurred when air was introduced slowly and twice as rapidly				6.26		5.87

While it is difficult to record the point of rupture of the intestine when the pressure is applied rapidly, I have endeavored to obtain some data on which a comparison may be made of the introduction of compressed air into a hollow viscus, both slowly and rapidly. The first specimen was tested in the regular manner and the result recorded. Several succeeding specimens adjacent to the first were tested with the pressure applied approximately twice as rapidly as in the first instance. The results as outlined in table 2, while meager and entirely too few from which to draw definite conclusions, are enlightening. It will be noted from table 2 that slightly less pressure is required to rupture the corresponding specimens when the pressure is introduced roughly twice as rapidly as in the first case. It is likely that there would be a still greater difference in the pressures required to rupture the intestine when the air is introduced at a relatively much greater rate as has been almost always the case in the reports in the literature.

The question has been raised as to whether the pressure required to rupture the intestine within the intact abdomen would be the same as that necessary to rupture it outside the body. In answering this it is necessary first to consider the relative intra-abdominal and external pressure. The intra-abdominal pressure as stated by Haven Emerson¹⁸ in the *Archives of Internal Medicine* in 1911 and referred to by Burton-Opitz¹⁹ in his textbook of physiology retains a value very close to zero during quiet respirations but of course, the active participation of the abdominal muscles in expiration gives a much higher value. In view of this there would seem to be very little if any difference between the pressure required to rupture the intestines inside or outside of the abdomen. Hence the average pressure of 4.07 pounds per square inch (table 1) the average found experimentally to perforate various portions of the alimentary tract outside the body represents approximately the pressure required to rupture the intestines within the intact abdomen.

PRACTICAL APPLICATION

The practical application of these data lies in the emphasis which they tend to produce on the necessity of care in the instrumentation in the field of proctology, the intrarectal manipulation in removal of impacted feces in the administration of the various kinds of enemas and in the handling of the intestines during surgical procedures as it is a fairly frequent experience of the surgeon to find the intestine lacerated or ruptured when handled by unskilled persons.

With the permission of Dr. Charles H. Goodrich, the following case of pneumatic rupture of the intestine is reported from the first surgical service of the Methodist Episcopal Hospital.

CASE 1—History.—J. L., a white man aged 49, single, a shiftless laborer and a heavy drinker for years was admitted to the Methodist Episcopal Hospital at 3:00 a. m. with a sharp, severe, epigastric pain of twelve hours' duration. His family history was irrelevant. For many years there had been a hernial protrusion in the midline of the epigastrium and one in the left inguinal region. A primary syphilitic lesion had been present twenty-two years before admission. Gonorrhea had been contracted several times. One eye had been injured and removed ten years before admission. The past history was otherwise unimportant.

The present illness began with a sudden, sharp, severe pain in the epigastrium twelve hours prior to admission, while the patient was working. He continued to work for one hour, at which time the pain became so severe that he went home to bed. Shortly afterward he vomited a small amount of greenish fluid. Following this, a dull aching sensation appeared throughout the abdomen with a persistent, severe epigastric pain. The bowels moved several times prior to the

18 Emerson, H. Intra-Abdominal Pressures, *Arch. Int. Med.* 7:754 (June) 1911.

19 Burton-Opitz, R. *Text Book of Physiology*, Philadelphia, W. B. Saunders Company, 1920.

onset of pain and a short time thereafter. He vomited several times during the twelve hours prior to admission. Anorexia was pronounced after the onset of pain.

About the time the epigastric pain began, the patient noticed that the protrusion in the upper part of the abdomen had increased in size, had become quite tense and was very tender. The left inguinal region had also become prominent. This was the history elicited before the operation. The next day, twelve hours after operation, the following additional history was obtained. While at work, the patient, desiring an enema, inserted a tube into his rectum. By mistake he turned on compressed air, and immediately experienced the pain described. The abdomen became large and breathing difficult.

Examination—On admission physical examination revealed a very muscular man, conscious, lying uneasily in bed, with marked pallor, pinched facies and anxious expression, slight cyanosis of the lips and finger-nails, cold and clammy skin and an alcoholic odor to the breath. He was evidently suffering from great pain. Respirations were grunting, at a rate of 26, and were chiefly costal. There were no abnormal pulmonary observations. The heart was slightly enlarged to percussion, and there was a blowing systolic murmur at the third left interspace. The sounds were of poor quality, somewhat irregular and at a rate of 90. The temperature by mouth was 100 F. The abdomen was greatly distended, moved only slightly with respiration and was extremely tense, and the umbilicus was almost obliterated. There was marked tympany throughout. There was no evidence of intra-abdominal fluid or of subcutaneous emphysema. About midway between the ensiform process and the umbilicus was a rounded, slightly bluish, nonreducible, tender protrusion the size of a lemon. The left inguinal ring was considerably enlarged, and through it protruded a nontender reducible mass of intestines. Rectal examination revealed considerable tenderness throughout. There was some fecal matter but no blood in the rectum. There were extensive scars over the shaft of the left tibia, a large one in the inguinal region and a small one on the glans penis. Otherwise the physical examination was negative. On admission, the leukocyte count was 11,600, 84 per cent polymorphonuclears and 16 per cent small mononuclears.

Operation—On the basis of the preoperative history and the elicited clinical signs, a diagnosis of strangulated epigastric hernia was made, for which an operation was begun thirteen hours and fifty minutes after the injury. The anesthesia was induced with nitrous oxide and oxygen and continued with ether. The operation consumed one hour.

A transverse incision was made in the epigastrium over the hernial mass. When the peritoneum was incised, a considerable quantity of gas with a fecal odor escaped with a whistling sound. The respiratory embarrassment and the cyanosis were immediately diminished. The abdomen became much less distended and the epigastric mass much smaller. Only a small portion of the greater omentum was found to be contained in the hernial sac. The neck of the sac, which was about 1.5 cm in diameter, was enlarged and the omentum was released. It was found not to be strangulated. At once it was apparent that the patient's symptoms and signs were not due to a strangulated epigastric hernia. The original incision was enlarged to about 17 cm in length and a longitudinal incision 12 cm in length was made from the center of the first, forming a "T."

The abdomen was explored. The serosa of the colon and small intestines was greatly injected and there was a small quantity of blood-stained fluid containing fecal particles in the pelvis. No free blood was found. The left inguinal

canal was enlarged, but did not contain any omentum or intestines. The sigmoid flexure and the lower portion of the descending colon were brought into the incision and were found to be collapsed. Beginning in the upper portion of the rectum and extending through the sigmoid flexure and the descending colon there was marked, fresh diffuse, subserosal hemorrhage, most extensive in the mesentery and in the mesenteric surface of the colon and rectum though extending well around onto the antimesenteric surface. The appendices epiploicae were also markedly hemorrhagic. There were numerous small scars throughout the sigmoid. Near the junction of the sigmoid flexure with the descending colon on the antimesenteric surface there were two longitudinal lacerations in the serosa and muscularis measuring 2 and 5 cm. in length and about 1 and 1.5 cm. in width. The larger of these was sutured with continuous plain catgut.

The extensive hemorrhage and the laceration of the wall suggested the previous introduction of compressed air into the rectum. In view of the presence of fecal particles and much gas in the abdominal cavity we felt certain that a perforation of the intestine had occurred, though none could be found after several minutes of searching. A rubber drainage tube was inserted in the lower angle of the incision and a cigarette drain was placed in the pelvis through a stab wound in the midhypogastrium. The abdomen was closed in layers with silk-worm gut reinforcement.

Course.—At the close of the operation the general condition of the patient was poor. Abdominal distention and vomiting of dark brown fluid gradually increased from the second day. No peristaltic waves were audible and no passage of fecal matter occurred through a rectal tube. Bronchopneumonia developed on the seventh day. From the third day, there was fecal discharge from the incision and increasing dehiscence of the wound with some evisceration of the underlying viscera. The rectal temperature ranged between 102 and 103 F., the pulse rate was 100, and the respiratory rate varied from 25 to 30. Gastric lavage was performed several times in the first few days and the depletion of fluid was cared for by hypodermocentesis. Sufficient morphine was given for relief from pain usually two doses of one-fourth gram (0.016 Gm.) in twenty-four hours. After operation the blood cells, blood chemistry and urine showed no appreciable deviation from the normal. The Wassermann reaction of the blood was negative. The blood pressure was 103 systolic and 68 diastolic. The patient's mentality remained clear, except for occasional flighty intervals, until shortly before death at 3:40 a. m. on the eighth postoperative day.

Autopsy.—An autopsy was performed, and the pathologist reported. All of the viscera of the abdomen were markedly matted together, and to the diaphragm and the lining of the abdominal cavity by a diffuse fibrinopurulent exudate and there was a large quantity of thick, yellow pus in the pelvis and other recesses of the abdomen. Underneath the hypogastric stab wound was a ragged, gaping opening 2 inches long in the convexity of the sigmoid near its junction with the descending colon, which communicated with the abdominal cavity and contained a mass of hardened feces. This opening was just adjacent to a short line of suture in the sigmoid. The rectum, sigmoid and descending colon showed numerous white, scarred areas scattered over their surfaces, and these portions of the colon, including the appendices epiploicae together with the mesentery, were markedly hemorrhagic. There was a left inguinal hernia, the sac of which measured 6 by 4 cm. The lungs were congested and nodular, suggestive of bronchopneumonia. The heart showed nothing abnormal. The liver, spleen and pancreas were much enlarged. The prostate contained small cavities, indicative of an old prostatic abscess.

Microscopically, sections of the lower lobes of both lungs showed areas in which the alveoli were filled with desquamated epithelium, pus cells and blood, the tubules of the kidneys showed some granular degeneration, and the liver presented granular degeneration and some fatty infiltration. Otherwise, the organs showed nothing of interest.

Diagnosis—The diagnosis was traumatic rupture of the sigmoid, general peritonitis, bronchopneumonia, chronic prostatitis and probably old syphilis.

This case is unique in that the pneumatic rupture of the intestine was associated with an epigastric and an inguinal hernia. The patient is the oldest (49 years) on record as having received this injury, the pressure of 2 pounds is the lowest so far reported as having caused this condition, and the patient is the first to give a history of this peculiar type of self-inflicted injury, not purely accidental. The patient mentioned by Duval, in 1921, was the first reported as having received an entirely intentional injury.

Dr Loyal A. Shoudy,²⁰ chief surgeon for the Bethlehem Steel Company, permitted me to present the following data on three cases of pneumatic rupture of the intestines which occurred in their plants.

1 A S, in the Elizabeth, N J, plant, was using an air hose to dust off his clothing, when J K, offering to help him, jokingly stuck the hose in the region of his fellow worker's rectum. A S fell in a faint and was rushed to the hospital, where Dr McCallion operated and found many ruptures of the intestines. The patient recovered (July 28, 1927).

2 An accident occurred in the Bethlehem plant in 1916. A workman, in fooling, placed an air hose near the rectum of a fellow worker (S V). The patient died the same day.

3 St. Luke's Hospital, Bethlehem, Pa., has a record (1927) of a worker who placed an air hose near the rectum of a fellow worker. The patient was operated on by Dr W P Walker and recovered.

Dr John J. Moorehead, director of the department of traumatic surgery, New York Post-Graduate Medical School and Hospital, New York, has given me permission to report the following case (which is not included in the statistics).

CASE 2—History—P M, a white man, aged 37, an Austrian, a repairman, was admitted to the hospital at 10 40 a m on March 18, 1928, complaining of pain in the abdomen and right shoulder of twenty-three hours' duration. On the day before admission, while the patient was bending over washing his face and hands at his place of work, a fellow employee jokingly placed the nozzle of a compressed air line, used to clean motors, against the clothing covering the patient's anus. The nozzle was held there for only a second. The air line was connected to two pumps, though the patient did not know the amount of pressure applied to his rectum. He felt a severe, sudden pain in the rectum and the lower part of the abdomen, became dizzy and fell to the floor. He vomited once after the ingestion of magnesia three hours after the accident. He took nothing else by mouth after the accident, though he had two bowel movements, which contained no blood. He voided once in the morning prior to admission, but no blood was seen in the urine.

²⁰ Shoudy, L. A. Personal communication to the author.

Examination—On admission, examination showed the patient to be in a moderate degree of shock pale and slightly restless the heart and lungs were surgically competent the abdomen was distended, round and markedly tender, with the maximum tenderness in the left lower quadrant, light percussion was painful liver dullness was obliterated, and there were signs of free fluid in the flanks.

A blood count taken before the operation showed 17,000 leukocytes, with 89 per cent polymorphonuclears.

Operation—A diagnosis of perforation of the intestine was made, and twenty-five hours after the injury Dr. Moorhead began an operation for relief from this condition. Through an incision in the right upper quadrant, the hepatic flexure of the colon was sutured to the peritoneum preparatory to establishing a subsequent colostomy, if necessary, but no opening was made into the colon. This incision was closed with a rubber tube drain in the wound. Through an incision in the left lower quadrant the sigmoid was found to contain three perforations, which were debrided. The larger of these was sutured and the others were left open. An iodoform gauze drain was inserted in the site of the perforations.

Course—The postoperative temperature and pulse reactions were slight, and on the sixth day the bowels began to move through normal channels. The patient was discharged on the forty-fifth postoperative day in excellent general condition with the abdominal wounds practically healed.

On June 19, 1930, two years after the patient was injured, he was readmitted to the Post-Graduate Hospital. For the first six months after his discharge, he felt only fairly well. He stated that during the preceding eighteen months he had grown somewhat weaker and had experienced general abdominal discomfort, which was exaggerated by exercise and the ingestion of food. He said further that he had taken only liquid food during the previous year, and that his stools had been loose and tarry, and had contained red blood since his discharge, his appetite had been poor, and he had felt some pain in his back, neck and extremities.

On readmission, physical examination gave essentially negative results. He appeared to be in excellent general condition. The blood count showed red cells, 4,310,000, hemoglobin, 82 per cent, leukocytes, 7,600, and polymorphonuclears, 63 per cent.

Sigmoidoscopy and proctoscopy revealed some evidence of perisigmoidal adhesions or angulation of the sigmoid. There was catarrhal proctitis with some mucus that extended well up into the sigmoid. Two ulcerative areas were present on the posterior anal wall.

At the end of twenty-four hours a gastro-intestinal series of roentgenograms showed a normal distribution of the meal, though the transverse and distal colon was narrow and spastic. The distribution in the distal colon was too irregular to permit a morphologic study. No evidence of obstruction was seen.

A barium colon enema showed moderate spasm at the junction of the descending colon and sigmoid. An S-shaped loop was noted at the colonic sigmoidal junction. There was no evidence of obstruction.

This patient's subjective complaints could not be verified by the objective observations. During his ten days in the hospital he ate a regular diet, his bowels were constipated, with no blood in the movements, he did not vomit, and he had no definite complaints. He had always been considered unstable mentally and emotionally and usually had borne the brunt of the jokes of his fellow workers. It was felt definitely that he was suffering from a marked neurosis and "compensitis." Though he was discharged in excellent general condition after an extensive study, every effort to return him to his work proved futile.

ETIOLOGY

The cause of this accident is the introduction of air under pressure into the oral cavity or the anus. Compressed air is used in the operation of pneumatic hammers and drills, dusting of machinery and barrels and in many other forms of commercial art. Unfortunately some of the workers, not realizing the devastating effect of the air, in a mood of joviality, direct the end of the nozzle toward the anus of a fellow worker. It is these practical jokers who have accounted for almost all of the injuries.

There are only four of the forty cases reported that I feel fairly certain were not the results of practical jokes. In the case herein reported, the patient himself introduced the nozzle into his rectum and turned on compressed air instead of water. The patient described by Jean was injured as a result of the explosion near the anus of a tube conveying compressed air. Petrin presented a case in which the esophagus was ruptured as a consequence of the worker falling while he carried a compressed air hose in his mouth, allowing the end of the hose to be released and the air to enter the oral cavity. In the case mentioned by Duval, the patient inflated his own rectum with a bicycle pump.

Generally, one or more layers of clothing were interposed between the nozzle and the anus, but this did not reduce the great power of penetration and deadly effect of the air to any appreciable extent. The nozzle was usually several inches from the anus, though in a few instances it was tightly pressed against the anus, and was said to be introduced into the rectum in four cases. In the first of these Stone suggested that in his patient the nozzle was introduced through the anal orifice, because the injuries to the bowel were such as to lead him to think, on account of the number and size of the rents, that the intestine had been nipped between the nozzle and the sacrum, though the latter showed no sign of injury. One case presented by Andrews, another by Duval and the one herein reported are the only others in which the nozzle was said to be introduced into the rectum.

In 1911, Andrews presented the most concise and logical explanation of the gross mechanics of this injury as follows:

I feel sure that at 50 to 125 pounds of pressure a gas would form a column several inches in advance of the tube, and would act almost like a solid body in forcing open the sphincter. The jet of a fountain can be made to support a good size ball of some weight, so the jet of air is more than ample to force open the levator and sphincter ani muscles and the soft pelvic floor. The nates and the pelvic floor form a funnel whose apex is the anus. All confined air expanding in this funnel will force open the gut without having the end of the pipe adjusted to the anus. With the voluntary contraction of the levator ani muscles the space between the buttocks would be narrowed and the funnel deepened thus confining the air laterally and leading it more quickly into the bowel.

The effect of the introduction of air would be greater with the patient in a stooping attitude a sitting posture, and when he is taken by surprise at which time the sphincter would be most relaxed and the intra-abdominal pressure at its lowest thus reducing the safeguard to a minimum in preventing the introduction of a foreign substance through the anal orifice.

Gant²¹ stated that the bowel has been ruptured several times by ignorant and careless physicians attempting to use pneumatic sigmoidoscopes. They have overdistended the intestine with the air or have forcibly pushed the instrument through the wall of the intestine.

MORBID ANATOMY

The pathologic changes found will depend on the pressure applied, its proximity and angle of application, the individual resistance of the tissues, the contents of the bowel and numerous other minor considerations. In general the changes may be divided into external and internal or those found at operation or necropsy.

External Changes—Two cases reported by Andrews in which autopsies were performed showed bruises about the anus. Another case (Bendixen and Blything) showed the tissues about the anus ecchymosed and the anal sphincter stretched so as to admit four fingers. Sparkman and Schwartz each reported a case in which there was bloody mucus on the rectal tube on withdrawal. Several writers have reported prominence of the inguinal canals. Subcutaneous emphysema was noted in seven cases. In general it was confined to the trunk. One of Jean's and another of Buchbinder's also showed the external genitals involved, and in the latter case the perineum was affected. In Hailes' case it extended from the eyebrows and lower part of the scalp down over the body to Poupart's ligaments, distorting the face and interfering considerably with the proper examination of the abdomen and chest. In Petrin's case, the emphysema extended over the chest down to the navel and on the arms almost to the elbows, and was found in the mediastinal tissues.

Changes Found at Operation and Necropsy—When the peritoneum is entered, there is generally an escape of considerable gas with a fecal odor. If there is no perforation of the intestine, the intestine is distended and there is no escape of gas on incision of the peritoneum. If it has been perforated, the intestine is generally collapsed.

Air has been found in the peritoneal cavity in several instances when no perforation could be located. This may be explained on the basis of observations which I have made on cadavers as a result of

²¹ Gant, S. G. Diseases of the Rectum, Anus and Colon, Philadelphia, W. B. Saunders Company, 1923, vol. 2, p. 464.

distention of various portions of the intestines by air. When the intestine ruptured on the mesenteric surface, the air gradually elevated the serosa for a considerable distance along the intestinal wall, both longitudinally and circumferentially, and finally broke through this thin layer of tissue at one or more very minute points, thus allowing the air to escape into the general abdominal cavity and leave no macroscopic evidence of its entry. Invariably in these cases it was necessary to immerse the specimen in a basin of water to locate the points of rupture.

Moynihan²² stated that "one sign alone is characteristic of the lesions of those portions of the bowel which are not wholly covered by peritoneum (parts of the duodenum and ascending and descending colon)—that is, emphysema." The appearance of the subcutaneous emphysema, as noted in several cases clinically, probably can be explained on the basis of my observations. Following the mesenteric rupture of the intestine, it is probable that the air dissects its way through the muscles and fascia without perforation of the serosa and enters the subcutaneous spaces to produce the clinical entity emphysema.

The rectum, various portions of the colon, the ileum, the mesosigmoid and the mesentery of the ileum and the esophagus have been reported ruptured. In all of these cases, except that mentioned by Duval, in which operation or autopsy was performed the distention resulting from the introduction of air into the intestinal canal was sufficient to produce lacerations of the outer coats and in many instances perforation of the mucosa.

The sigmoid flexure is by far the most frequently ruptured, which is explained by the fact that it forms the first barrier to the rushing air. It is attached by a rather long mesentery in contrast to the short or absent mesentery of the descending colon, and forms a somewhat semicircular trap for the entering air, which, similar to a solid body, tends to maintain its velocity forward in a straight line. The air thus comes in forcible contact with the sigmoidal wall where the latter tends to form almost a right angle juncture with the descending colon, when pressure is applied within its lumen.

The perforations noted clinically usually have been single, though a few have been multiple, and they have varied in size from one that was scarcely visible to one 6 inches (15.24 cm) in diameter, as noted by Bendixen and Blything. The lacerations of the serosa and muscularis usually have been multiple and extensive, due to the fact that it is the outer coats that rupture first during the distention, thus allowing the mucosa to herniate through and eventually perforate at a higher pressure.

²² Moynihan, B. *Abdominal Operations*, Philadelphia, W. B. Saunders Company, 1914 vol 2, p. 80.

than is required to tear the serosa or muscularis. Several observers have noted these lacerations and perforations to be chiefly along the longitudinal bands on the antimesenteric surface of the colon.

Andrews reported one case in which the patient died of general peritonitis, in which there was a rupture of all of the layers of the colon, except the mucosa from the rectum to the appendix. In one case Bendixen and Blithing observed extensive lacerations of the sigmoid (7 inches [17.78 cm]) the descending and ascending colon, the mesentery of the ileum and of the ileum itself, and a 6 inch perforation near the hepatic flexure. A perforation at the base of the cecum was reported by Cotton. One case (Hailes) presented a superficial laceration of the lower end of the colon, a 3.7 cm tear in the hepatic flexure, a markedly hemorrhagic colon, a collapsed right lung and bloody fluid in the right pleural cavity. Petrin's case presented a 6 inch longitudinal rupture of all of the coats of the esophagus with emphysema of the mediastinal tissues. Hemorrhage and ecchymoses are to be expected wherever there is damage to the intestinal wall. Several cases, particularly Hailes, Schwartz, Andrews' and mine have presented marked diffuse, subserosal hemorrhages, most extensive in the mesentery and mesenteric surface and extending well around onto the antimesenteric surface of the colon and involving the appendices epiploicae. Duval reported a case in which the patient had markedly inflated his colon with air by using a bicycle pump. No laceration of the wall of the intestine could be located at operation, which was performed under the provisional diagnosis of total megacolon.

POSTOPERATIVE COMPLICATIONS

These complications have been mentioned particularly in only three instances, and it is interesting to note that these three patients recovered.

Andrews reported a case in which Fletcher repaired an extensive laceration of the sigmoid, which later caused intestinal obstruction due to a narrowing, for which a colostomy was performed with a subsequent resection of the constricted portion. A ventral incisional hernia was repaired.

In their case Block and Weissman reported the suturing of extensive lacerations and a perforation in the upper part of the rectum and lower end of the sigmoid and the performance of a jejunostomy. Acute intestinal obstruction developed as a result of the constriction of the injured area, for which an entero-enterostomy was performed. Acute epididymitis developed, from which the patient recovered.

Hays' case presented extensive lacerations of the upper part of the rectum and lower end of the sigmoid and a perforation of the lower end of the sigmoid, which were repaired, and the sigmoid was sutured to

the anterior peritoneum preparatory to a colostomy, which was performed on the first postoperative day because of distention, which increased to such an extent that a cecostomy was done on the second day after the operation. Drainage through the cecostomy became so free that it was evident that the patient would expire if something was not done to stop the rapid passage of fluid through this opening. The Barnes dilator was employed successfully to stop the drainage of fluid, and the patient improved markedly and recovered. Hernias developed in the abdominal incisions and were subsequently repaired, as was also the incision for the cecostomy.

ROENTGENOLOGY

A roentgenographic study was made by Morris five months after an operation on a patient showing an uneventful recovery and excellent health in the interim. This patient presented extensive lacerations of the serosa and muscular coats of the cecum, ascending colon and the sigmoid flexure, and a large quantity of blood in the pelvis and among the coils of intestines. A six hour examination showed a poor filling of the cecum and ascending colon. The contour was irregular and deformed. There were evidently numerous adhesions in the vicinity of the cecum and ascending colon. The sigmoid appeared to be normal except for a narrowing in the first portion. No other cases except Dr. Moorehead's incorporated here, have been reported as having been studied by the roentgen ray.

SYMPTOMS AND SIGNS

The symptoms and signs, though dependent on the degree of injury, are essentially the same for all cases, and may be appropriately divided into those of a local and those of a general nature.

Local (Abdominal) Symptoms—There is usually a sudden onset of a constant, sometimes colicky, very severe pain in the lower part of the abdomen, which the patient may be unable to localize more concisely. He complains of great difficulty in breathing. The most marked feature of this condition is the enormous distention of the abdomen, which extends into the flanks, with obliteration of abdominal dulness. There is marked hyperresonance. The umbilical depression is greatly diminished or absent, and the inguinal canals are often prominent. The abdomen is rigid and tender throughout, with a maximum over the injured viscus. If the patient is seen within a very few hours after the accident palpation of the abdomen does not produce the sensation of a diffuse peritonitis but this may be superimposed several hours after the injury.

General Symptoms—The patient generally shows a marked degree of shock; the skin is cold and clammy; he is usually conscious though

many times unconscious, and his facies is pinched and presents an anxious expression. A moderate or marked degree of cyanosis and nausea and vomiting are usually present. The thighs are flexed on the abdomen. The respirations are rapid (average of 35 in the eight cases in which the rate was given), labored, grunting and costal, as a result of pressure on the diaphragm. The heart sounds and the pulse rate are accelerated and of poor quality. The rate averaged 119 in the eleven cases in which the pulse was stated to range from 74 to 190. The temperature is usually subnormal, except in cases of several hours' duration, in which peritonitis has manifested itself. Two cases of twelve and eighteen hours' duration prior to operation showed temperatures of 100 and 102 F.

Buchbinder's case manifested clonic spasms of the muscles of the trunk. Subcutaneous emphysema was noted in seven cases, and was confined chiefly to the trunk.

DIAGNOSIS

With or without a history of the introduction of compressed air into the rectum, one should be able to make a diagnosis of this condition. In a case complicated by an associated hernia the diagnosis is made more difficult. If the patient shows severe shock, cyanosis or pallor, great respiratory embarrassment, rapid and thready pulse, marked distention, hyperresonance and extreme tenderness of the abdomen, with obliteration of the umbilical depression and abdominal dulness, especially when this is found unassociated with a hernial mass, one should be able to make the correct diagnosis. With the history of the introduction of compressed air into the rectum, the diagnosis should be evident. If this history is unavailable and the surgeon is unwilling to make a definite diagnosis, he should at least label it an "acute abdominal condition" and proceed immediately with a laparotomy, provided the condition of the patient permits operative intervention.

This condition, however, must be differentiated from other acute abdominal conditions, and among the more important of these, one must consider general peritonitis, volvulus, intussusception, ileus with or without perforation, ruptured gastric, duodenal or typhoidal ulcer, strangulated hernia, stab wound, gunshot or other traumatic perforations and ruptured lung and fractured rib with the presence of subcutaneous emphysema.

MORTALITY

The general mortality in this series of forty-four cases is 56.81 per cent. The ages in this series, as stated in twenty-nine, ranged from 13.5 to 49 years, averaging 23.8 years, with only six patients 35 or more years of age. The operative mortality is 44.82 per cent (twenty-nine patients were operated on, with sixteen recoveries and thirteen

deaths) Of the operative recoveries, the time elapsing between the occurrence of the injury and the institution of operative proceedings, as stated in eight of the fifteen cases, ranged from one hour and fifty minutes to five and one-half hours, and their ages were from 14 to 45 years, with six not given, making an average of 27.6 years. Relative to the operative deaths, ranging from 13.5 to 49 years, with an average of 23.7 years, with four not given, the time after injury that operation was begun, as stated in seven of the twelve cases, ranged from about three hours in Stone's case, in which only a paracentesis abdominis was performed ante mortem, to four days, in one of the cases reported by Bendixen and Blything, in which the patient was brought to the operating room in a moribund condition.

The nonoperative mortality is 80 per cent (of fifteen patients not operated on, twelve died). The ages of those who died after operation ranged from 16 to 27 years, with the ages of four of the twelve not given, making an average of 21.3 years. The three cases in which the patients recovered without operation were: One reported by Andrews with the age not given, in which live steam was introduced into the rectum, that of a boy, 16 years of age, mentioned by Bendixen and Blything, who recovered and returned to work shortly after the accident, and another recorded by Fauquez, in which a boy of 15 suffered from distention of the colon but recovered in a few days. The symptoms and signs in these cases were said to be such as to warrant a clinical diagnosis of rupture of the bowel.

Of the seven cases in this series showing subcutaneous emphysema, the mortality is 57 per cent.

PROGNOSIS

The prognosis is grave with or without operative intervention but the outlook is distinctly better when an operation is performed. The results herein recorded suggest that if a patient is operated on within six hours after the injury his chances of recovery are considerably better than if a greater time is allowed to elapse. Age seems to exert no particular influence on the results. It is of interest to observe that this condition is one of late adolescence and early adult life, the average age of the patients being 23.8 years.

TREATMENT

Operative Treatment—The treatment "par excellence" for the abdominal condition is immediate operation provided the general condition of the patient will permit. An intraspinal anesthesia is probably the most suitable for this condition. If it is considered better judgment to defer the laparotomy general supportive measures should be employed to improve the general condition of the patient. An immediate para-

centesis abdominis should be performed in cases of marked distention to release any air contained in the abdominal cavity, thus relieving the pressure on the diaphragm. A physician administering emergency treatment should not hesitate to perform a paracentesis and release the air slowly. Many times following this procedure the condition of the patient will improve markedly and thus facilitate a subsequent laparotomy with a better prognosis.

The incision of choice is a left lower rectus or a low median line. The exploration of the abdomen should include as minute scrutiny as possible of the entire colon, the lower part of the ileum and the mesentery. The character of any fluid contained in the abdomen and the presence or absence of any gas with a fecal odor will suggest the severity of the injury.

If there is only a small amount of damage to the serosa and muscularis or a small perforation, these may be repaired very easily and quickly. Obviously, if there is great damage and repair is impossible, resection of the injured portions and the establishment of a colostomy are indicated. If the condition of the patient is extremely poor, it may save time and even the patient's life to bring the injured intestine into the incision as a colostomy (Andrews). More frequently, however, it would be wiser to complete the repair. When a resection is necessary and sufficient viable and movable intestine can be obtained, one should perform a lateral or end-to-end anastomosis. When an anastomosis is impossible, a colostomy should be established. One should not hesitate to establish an artificial anus above the injured area, especially when the damage has been extensive, in order to relieve the pressure over the affected portion, which has been repaired.

Whether to repair the injury and establish drainage higher up, perform a resection and do an anastomosis, establish an artificial anus or bring the injured portion into the wound as a colostomy is the responsibility of the surgeon and depends on the amount of damage to the intestine and the general condition of the patient.

The treatment indicated for injuries resulting from the oral introduction of air into the alimentary canal is determined by the judgment of the surgeon, depending on the degree of injury thought to be present and the condition of the patient. In general, it is palliative.

Postoperative Treatment—This is largely a matter of symptomatic treatment, and it is necessary to deal separately with each condition as it arises. The patient preferably should be placed in the Fowler position. Distention, due principally to a parietic condition of the bowel, is to be expected, and may be relieved when feasible by the use of a rectal tube, milk and molasses enema, glycerin, turpentine and other enemas. Fluid depletion may be restored by the use of physiologic solution of sodium

chloride introduced by hypodermoclysis, by slow proctoclysis when possible and by the administration of physiologic solution of sodium chloride or dextrose solution intravenously

CONCLUSIONS

1 Compressed air is used extensively in industrial arts, and it is important to educate the employees concerning its deadly, penetrative powers, especially since almost all of these injuries are caused by practical jokers

2 Clinically, the sigmoid is the viscus most frequently ruptured

3 Experimentally, the rectum supports the greatest pressure, and the sigmoid, ileum, esophagus, jejunum, transverse colon, cecum and stomach decrease in strength in the order in which they are mentioned

4 The outer two coats of the colon generally rupture along the longitudinal bands, this is followed by marked herniation and subsequent perforation of the mucosa on the antimesenteric surface. In the remainder of cases the mucosa perforates on the mesenteric surface of the intestine

5 In the small intestine, in somewhat more than 50 per cent of the cases, all of the layers perforated simultaneously on the antimesenteric surface, with slight laceration of the outer two coats and very little herniation of the mucosa. In the rest of the specimens, mesenteric ruptures occurred

6 A higher pressure is required to rupture portions of the alimentary tract in children than in adults

7 The average pressure required experimentally to perforate the various parts of the intestinal canal both within and without the abdomen is approximately 4.07 pounds per square inch

8 Less pressure is required to rupture the intestine when the air is introduced more rapidly

9 The general mortality is 56.81 per cent, the operative mortality, 44.82 per cent and the nonoperative mortality, 80 per cent

10 Early release of intra-abdominal pressure and laparotomy for proper surgical disposition of the intestinal injuries offer practically the only hope for recovery of the patient

Dr. George A. Bullwinkle made the accompanying sketches. Lieutenant Commander Fennimore S. Johnson, M.D., U.S.N. prepared the microscopic sections, Prof. H. W. Farwell, physicist, Columbia University, supplied the physical computations.

PRIMARY MYELOGENOUS SARCOMA COMPLICATING CYSTIC DISEASE OF THE HUMERUS

REPORT OF A CASE⁴

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AND

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Primary tumors of the bone characterized histologically by an unorganized growth of round cells, without appreciable intercellular substance occupy an uncertain position among malignant neoplasms of the bone. In the literature one may find such varied designations of these tumors as "solitary myelomas," "undifferentiated osteogenic sarcomas," "round cell sarcomas of bone," "endotheliomas," "cellular medullary tumors," "embryonal tumors of bone marrow" and "myelosarcoma." Ewing's sarcoma, apparently a homogeneous clinical entity, has but recently¹ been segregated from this ill-defined category of tumors.

We have recently studied the available literature on primary tumors of the bone in connection with a confusing tumor of the humerus, removed from a patient of one of us (H. McK.), which clearly originated as a complication of preexisting cystic disease of the same locality. This tumor had microscopic characters in common with the group of myelomas, while a disseminated scanty fibrous, hyaline and osteoid intercellular substance and certain of its gross characteristics allied it to the osteogenic sarcomas. In view of these peculiarities, we believe that a description of this tumor and a discussion of its place among primary tumors of the bone will be of interest in the general study of sarcomas of bone.

Cystic disease of the bone is believed rarely or never to undergo malignant change into primary sarcoma of the bone. In the literature, we have found one such case reported by Helbing². Beck,³ in com-

⁴ Submitted for publication, Aug. 12, 1930.

^{*} From the Norman Bridge Pathological Laboratory of Rush Medical College, and the Surgical Service of St. Joseph's Hospital.

¹ Ewing, J. Endothelial Myeloma of Bone, *Proc. New York Path. Soc.* **24** 93, 1924. Kolodny, A. Bone Sarcoma, *Surg. Gynec. Obst.* **44** 1-210, 1927, supp., part 2. Copeland, M. M., and Geschickter, C. F. Ewing's Sarcoma. Small Round Cell Sarcoma of Bone, *Arch. Surg.* **20** 246 (Feb.) 1930, The Nature of Ewing's Tumor, *ibid.* **20** 421 (March) 1930.

² Helbing, quoted by Beck.

³ Beck, C. Ueber achte Cysten der langen Rohrenknochen, *Arch. f. klin. Chir.* **70** 1099, 1903.

menting on Helbing's report, stated that if the roentgenograms are examined carefully, some sign of malignancy may always be found in cases in which the condition later becomes unquestionably malignant. The latter author cited a single case from his experience with "107 cases of osteosarcoma" which was confused with a cyst of the bone, but in which a slight break in the periosteum could be demonstrated. Bloodgood⁴ stated that most central lesions of the bone are either giant cell tumors or osteitis fibrosa, said to be but phases of the same pathologic process, and that the central malignant tumors are almost exclusively metastatic tumors, myelomas or central chondromyxosarcomas. Recently, Geschickter and Copeland⁵ advanced convincing proof that cysts of the bone, which usually are either giant cell tumors or osteitis fibrosa are always benign. These authors stated that proved cases of metastasizing giant cell tumor are instances of osteogenic sarcoma of the chondroblastic series containing giant cell osteoclasts in response to cartilage formation. However, the two cases cited by Wanke⁶ seem to be valid exceptions illustrating acquired malignancy in a previously benign giant cell tumor.

Instances of solitary primary malignant tumors of the bone composed exclusively of cellular elements resembling the round cells of normal bone marrow are rare. Kolodny⁷ stated that only one case of solitary myeloma has been reported in the Registry of Bone Sarcoma of the American College of Surgeons. Solitary myelomas of the cranium are said to have been found by Morax⁸ and Ewald⁹ and by Riser and Sorel,¹⁰ and of the ilium by Greengough, Simmons and Harmer¹¹ (case 11), but the conclusiveness of these observations is somewhat clouded by the lack of a complete autopsy in each case. Shaw¹² reported a solitary myeloma of the humerus following a frac-

4 Bloodgood, J. C. How to Diagnose and Treat a Bone Lesion. I. Central Lesions, *J. Bone & Joint Surg.* **8** 471, 1926, Central Sarcoma of Bone, *ibid.* **9** 217, 1927.

5 Geschickter, C. F. and Copeland, M. M. Recurrent and So-Called Metastatic Giant Cell Tumor, *Arch. Surg.* **20** 713 (May) 1930, Tumors of the Giant Cell Group. A Pathologic Entity, *ibid.* **21** 145 (July) 1930.

6 Wanke, R. Ostitis fibrosa und Sarkom, *Deutsche Ztschr. f. Chir.* **201** 358, 1927.

7 Kolodny (footnote 1, second reference).

8 Morax, M. Myelome orbitaire et cramen, *Presse med.* **18** 806, 1910.

9 Ewald. *Wien klin. Wchnschr.* **10** 169, 1897.

10 Riser and Sorel, R. Plasmocytome intracranien avec paralyses unilaterales multiples. *Ann. d. med.* **26** 385 1929.

11 Greengough, R. B., Simmons, C. C. and Harmer, T. W. Bone Sarcoma. An Analysis of the Cases Admitted to the Massachusetts General and Collis P. Huntington Memorial Hospitals from 1911 to 1921. *J. Orthop. Surg.* **3** 602, 1921.

12 Shaw, A. F. B. A Case of Plasma Cell Myeloma. *J. Path. & Bact.* **26** 125 1923.

ture that had been treated by curettage and bone graft, in which complete recovery had been made Rogers¹³ and Geschickter and Copeland¹⁴ each recorded a case of similar solitary myeloma of the femur. Another solitary myeloma of the humerus is to be found reported by Greengough, Simmons and Harmer¹¹ (case 20). Ewing¹⁵ stated that he observed solitary myeloma of the tibia and femur, but he did not describe his cases. Multiple myeloma, while a rare disease, is encountered with greater frequency, and is more familiar. Accounts of this multiple skeletal disease with summaries of the literature and bibliographies are given by Verse,¹⁶ Wallgren,¹⁷ Geschickter and Copeland¹⁴ and by many others.

Undifferentiated osteogenic sarcomas (Codman¹⁸), tumors that microscopically are "composed of round cells which show no tendency to form any known structure or tissue" are uncertain in their right to belong to this class of malignant tumors. As Codman further stated "These tumors are round cell sarcomas occurring in bone and from their position are classed as bone sarcomas, not because they are known to have been derived from bone or bone elements." Tumors described as undifferentiated osteogenic sarcomas are to be found among the case reports of Buerger¹⁹ (cases 3, 11 and 12), MacGuire and McWhorter²⁰ (cases 25, 26 and 27), Connor²¹ (cases 10, 11, 45 and 49) and by Coley and Coley²² (case 48). A few of these cases demonstrate definite affinities with the recognized types of osteogenic sarcoma by the presence of quantities of "spindle cells," while the remainder are similar to alleged solitary myelomas described by other authors. It is certain that these tumors do not comprise a homogeneous group.

13 Rogers, H. A Case of Solitary Plasma Celled Myeloma, *Brit J Surg* **17** 518, 1930

14 Geschickter, C F, and Copeland, M M. Multiple Myeloma, *Arch Surg* **16** 807 (April) 1928

15 Ewing, J. A Review and Classification of Bone Sarcomas, *Arch Surg* **4** 485 (May) 1922

16 Verse. Ueber Plasmozytome und myelomartige Wucherung des Knochenmarkes, *Verhandl d deutsch path Gesellsch* **15** 62, 1912

17 Wallgren, A. Ueber die Natur der Myelomzellen, *Virchows Arch f path Anat* **232** 381, 1921

18 Codman, E A. Bone Sarcoma, New York, Paul B Hoeber, Inc, 1925

19 Buerger, L. Bone Sarcoma, *Surg Gynec Obst* **9** 431, 1909

20 MacGuire, C J, and McWhorter, J E. Sarcoma of Bone. An Analysis of Fifty Cases, *Arch Surg* **9** 545 (Nov) 1924

21 Connor, C L. Endothelial Myeloma. Ewing, *Arch Surg* **12** 789 (April) 1926

22 Coley, W B, and Coley, B I. Primary Malignant Tumors of Long Bones, *Arch Surg* **14** 63 (Jan) 1927

REPORT OF CASE

History—Miss E S, aged 65, a patient of one of us (H McK), who for years had been employed only with her own housework, entered St Joseph's Hospital on Oct 1, 1929, for care of a refractured arm. In March, 1929, she had sustained a fracture in the distal one third of the left humerus as the result of a light fall over the edge of a rug at her residence. The patient stated that she definitely felt the arm "give way" before striking the floor. For about a year previous to this time she had experienced intermittent vague pains in the region of the left elbow. A roentgenogram (fig 1A) taken at the time of this first fracture explained the occurrence of the break after such minor violence, there

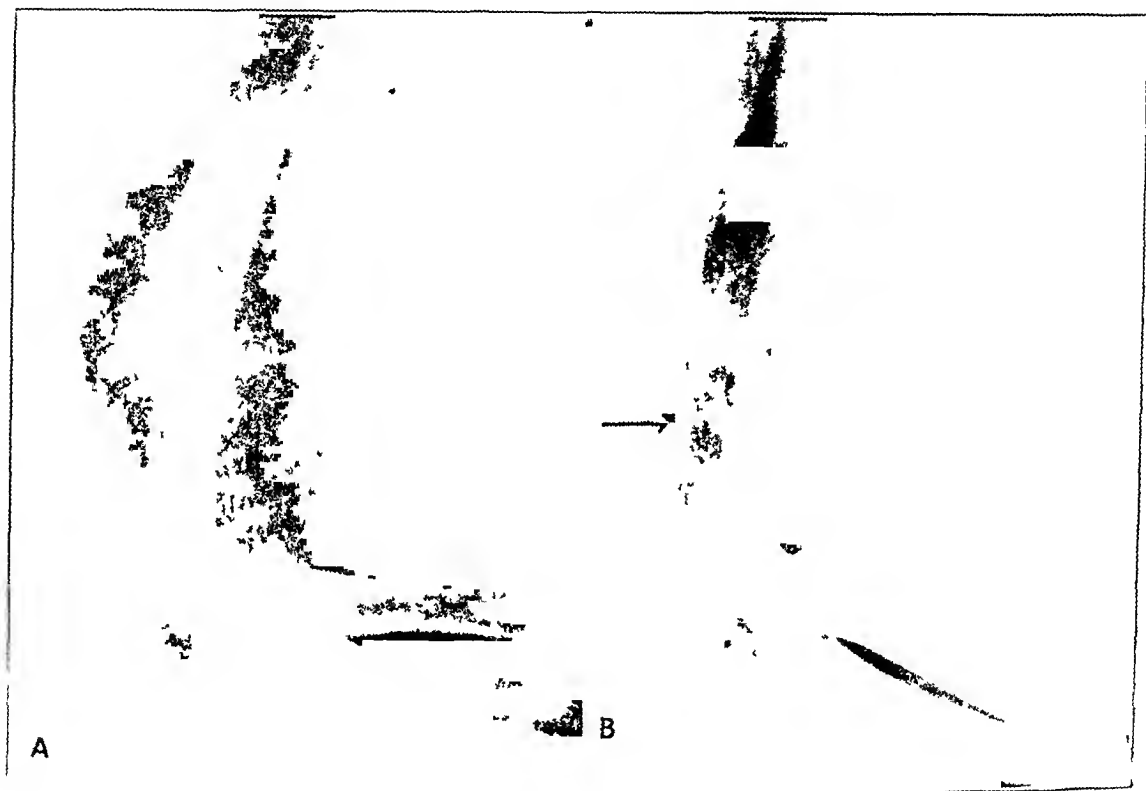


Fig 1—A, roentgenogram of the left humerus taken on occasion of patient's first pathologic fracture, B, roentgenogram of the left humerus taken at the time of the second pathologic fracture. The arrow indicates the site of biopsy, a section of which is shown in figure 2.

was a circumscribed zone of rarefaction with long axis parallel to the shaft of the left humerus, which had left only a thin plate of cortex in the distal part of this bone. The appearance of this picture was consistent with that of a benign solitary fibrocystic lesion. In a roentgenogram of the pelvis and upper half of both femurs, taken at this time, no fibrocystic changes were seen in these bones. Following five weeks of immobilization, the patient regained full function of the arm but intermittent pain, slightly more severe than previously, remained. About September 1, while drying dishes in her home, she suffered a spontaneous fracture at the same site which was treated temporarily by immobilization in a sling as this relieved the pain somewhat. Nothing further was done until the

patient entered the hospital. No other facts of possible significance were obtained from her past history, except that she had suffered for years from chronic "rheumatoid" pains on the right side from the hip to the knee.

Examination—Physical examination revealed nothing inconsistent with her age except locally in the left arm, where edema of the arm and forearm and brownish pigmentation about the elbow were seen. Some crepitus was elicited in the distal third of the arm, and pain on pressure was evident over the same area. Examination of the blood on admission showed only a mild secondary anemia, with normal coagulation time. There were 4,320,000 erythrocytes and 5,350 leukocytes in the peripheral blood. Hemoglobin was 70 per cent. The differential enumeration of leukocytes showed polymorphonuclear neutrophilic leukocytes, 66, small lymphocytes, 20, large lymphocytes, 8, and "transitional cells," 6 per cent. The Wassermann and Kahn reactions were both negative. The blood pressure was 165 systolic and 90 diastolic. Only a trace of albumin was found in an otherwise normal urine. The temperature on admission was 98.6 F, but notable was the fact that from the second day following admission until discharge and after readmission on December 31 up to subsequent amputation of the arm, the patient had a persistently subnormal temperature, averaging from about 96.4 to 97 F, which rose from 1 to 1.5 degrees nearer normal after the amputation. After entrance into the hospital, the patient still complained of persistent pain. Roentgen examination (fig 2) made just after entrance to the hospital demonstrated the same cystic lesion in this left arm as was discovered on the occasion of the patient's first fracture six and a half months previously, when she was attended by another physician. There was, in addition, an irregular transverse line of increased density, and on one side of the shaft of the humerus almost continuous with the previously mentioned line was a slight elevation of the periosteum. Elsewhere, the contour of the cystic lesion was even and regular. The possibility of a malignant tumor of the bone was entertained, and biopsy was done uneventfully under general anesthesia on October 17. The shaft of bone was sampled near the insertion of the triceps, posteriorly, at approximately the location indicated by the arrow in figure 1B. The curetted bone was described by a pathologist as a normal bone spicule, without inflammation or tumor. On reviewing these sections later, we discovered a few scattered foci of slightly pleomorphic cartilage cells (fig 2). An operative diagnosis of cyst of the bone was made at this time. Between October 9 and November 8, the patient was given four deep roentgen radiations to the distal two thirds of the left humerus in the hope of preventing metastasis.

The patient stated that she obtained union and partial function of the left arm after leaving the hospital in November, even the pain being but trifling. About December 24, while dressing herself, she again suffered a spontaneous fracture with a subsequent amount of pain comparable to the previous spontaneous fracture. About three days later she was seized with a sudden agonizing pain in this arm, so severe as to cause her to cry out. These new intense pains continued intermittently until and after the patient's reentry to the hospital on December 31. The temperature and results of the blood examination and urinalysis were essentially insignificant on readmission and subsequently, with the exception of the persistent subnormal temperature, already described, and an abnormally large proportion of "transitional cells" among the blood leukocytes, on one occasion 6 and on another 18 per cent.

Roentgen examinations at this time revealed in the left arm (fig 3) changes suggestive of malignancy and a fracture, probably pathologic. There were no

changes in the other bones, including the skull and pelvis, ribs and spine, except slight arthritic changes in the head of the right femur. A second biopsy was done through the old operative scar on the lower posterior aspect of the left arm, on Jan 8, 1930. Immediately on completion of the incision through the thinned fibers of the triceps muscle, a soft grayish tumor mass was found on the outside of the bone. An operative diagnosis of sarcoma of the lower end of the humerus was made, and the wound was closed. Examination of a portion of the tumor tissue was made by a pathologist, who reported "a highly malignant bone tumor, probably a primary sarcoma." Dr. E. R. Le Count later concurred in the opinion on the malignancy of the tumor.

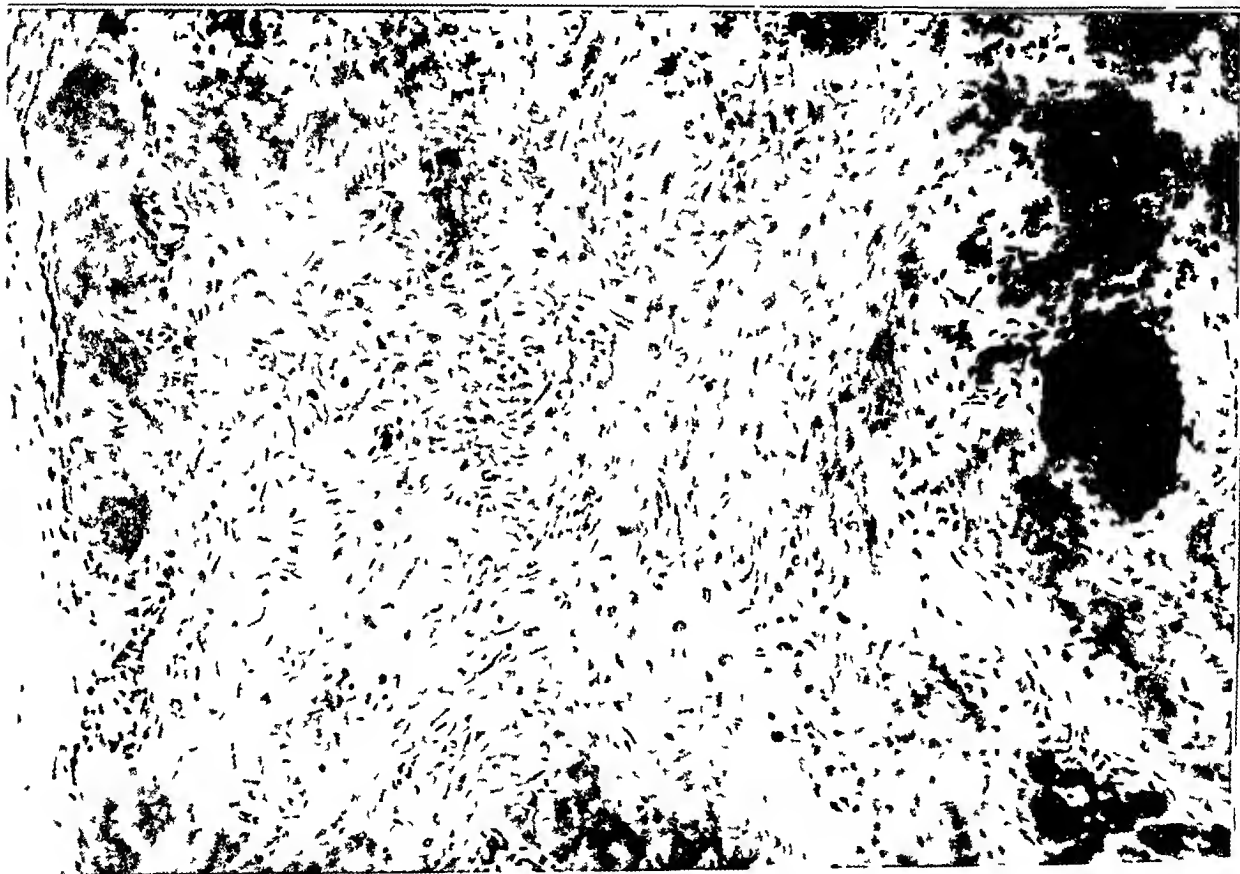


Fig 2—Photomicrograph taken of an area of pleomorphic cartilage cells found in biopsy sections done at about the time of the roentgenogram of figure 1B. Reduced from a magnification of $\times 160$.

Operation—An amputation was approved by the patient and was done on January 25, under general anesthesia. A preoperative roentgenogram of the thorax revealed a circumscribed nodule with a dense periphery in the upper left side of the chest near the apex, which was probably responsible for the observed displacement of the trachea to the right and for the slight fulness of the medial part of the left infraclavicular space. The patient stated that the latter had been present for years. The nature of this nodule was not definitely decided, except that it undoubtedly did not represent metastasis. Subsequent events proved this

to be true. The patient recovered without mishap from the amputation and was discharged from the hospital on February 8 in good condition. The patient has been in excellent general condition since the operation. At this time, twelve months following amputation, there is a local recurrence but no systemic metastases. Examination of the amputated specimen was begun three and one-half hours after completion of the amputation.

Macroscopic Examination—The amputated left arm was still warm and soft. The soft parts were cut through about the middle of the arm, the humerus 8 cm nearer the shoulder. The intact forearm and hand were attached. The skin of the upper part of the arm was smeared with blood. About the elbow, the skin



Fig 3—Roentgenogram of the left humerus taken at the time of patient's third pathologic fracture. Obvious signs of malignancy are present in this picture.

was stained with iodine in a zone from 5 to 8 cm wide. The distance from the olecranon to the tip of the styloid process of the ulna, along the skin, was 26 cm, that from the tip of the styloid process of the radius to the tip of the index finger was 16 cm. The width of the palm at the first distal transverse furrow was 77 mm. The maximum thickness of the hand was 22 mm at the base of the hypothenar eminence. The skin of the palm was smooth, soft, pliable and wrinkled only by the usual creases. That of the dorsum was also smooth, soft and pliable, but was a faint yellowish brown, slightly wrinkled and abnormally motile over the underlying tissues. The skin of the forearm not discolored by the yellow

referred to, was brownish yellow and finely mottled in places with a slightly darker color, and was smooth, soft, pliable and not wrinkled. There was an abundance of subcutaneous fat in the forearm. The width of the wrist at the level of the styloid process of the ulna was 57 mm. The width of the forearm at the elbow crease, with the arm in full supination and at as extreme extension as possible, was 105 mm. A full range of normal motion was possible at the wrist, and at all metacarpophalangeal and interphalangeal joints. At the elbow, extreme extension lacked from about 35 to 40 degrees of approaching a straight line, and forced flexion established an angle of only from 95 to 100 degrees between the arm and forearm. Supination could be completed, but forced pronation would bring the forearm to only about half the extent of normal complete pronation. The skin of the arm was smooth, soft and pliable, but was streaked with dried blood. There was even more subcutaneous fat in the arm than in the forearm, and the skin had about the normal amount of motion over the underlying parts. Externally, no abnormal structures could be felt beneath the skin of the forearm, hand, fingers or thumb. The maximum width of the arm was 125 mm at 4 cm proximal to the elbow. The circumference at the same level was 37 cm. A hard tumor was in the distal part of the arm, close to the elbow. This swelling had a limited amount of independent motion, and crepitated against the proximal parts of the humerus. The tumor projected externally, but slightly more on the internal aspect. The circumference of the arm at the edge of the skin made by amputation was 35 cm. Here the subcutaneous fat was abundant, golden yellow and from 22 to 42 mm thick. A small amount of divided muscle projected about 3 cm beyond the skin, and still more proximal an almost denuded apparently normal humerus extended 5 cm. The severed nerves and blood vessels presented at the site of amputation. The exposed tissues were soft and pliable, and no abnormal structures or tissues had been bared by amputation.

When the skin of the arm and forearm was cut there was from 10 to 15 cc of clear fluid in the subcutaneous tissues of the forearm. The abundant subcutaneous fat about the tumor was from 16 to 33 mm thick, in the middle of the forearm from 14 to 22 mm, and in the wrist, only from 1 to 6 mm. The weight of the skin of the arm and forearm, with this fat, was 1250 Gm. The median nerve with the brachial artery and venae comites ran over the front of the tumor, the nerve being slightly flattened and compressed to about half of its diameter. The brachial artery ran between the median nerve and the tumor in a shallow groove from 2 to 6 mm deep, and gave off several fairly large branches into the anterior capsule of the tumor. The artery throughout its course was completely collapsed and contained nothing within its lumen. The venae comites contained a few drops of fluid blood. The ulnar nerve ran over the dorsomesial aspect of the tumor and descended abruptly medial to the olecranon, being pushed ventrally from its normal position. The musculocutaneous nerve was entirely free from the tumor mass. Two grayish nodules one 18 and the other 23 mm in diameter projected into the subcutaneous fat, between the muscular septums in the medial bicipital sulcus. Over a large part of the tumor mass the ulnar nerve was flattened to a varying extent the maximum being about twice the normal diameter of the nerve. The radial nerve descended over the ventro-external surface of the tumor beneath the muscularis brachialis. This nerve was much flattened and compressed for 6 cm largely on the front and distal surface aspect of the tumor and then passed into the forearm. The muscles of the arm surrounded the tumor except at the two places described and were all firmly adherent on their under-surface to the capsule of the tumor. The muscularis

biceps brachii seemed to be little affected. The muscularis brachialis was markedly compressed and adherent to the outside of the tumor. The muscularis triceps brachii dorsally was somewhat atrophied. The common tendon of insertion of the long and medial heads of this muscle and the fibrous band between them filled a definite longitudinal furrow 50 by 10 by 5 mm in the dorsal part of the tumor. Here the tumor seemed to have been prevented from encroaching on the extreme dorsal part of the arm. The color of all these muscles was the same as the muscles elsewhere, a deep reddish brown. The circumference of the tumor at the level of the previous measurements was 27 cm. It was incompletely surrounded by a tough fibrous capsule, distinct anatomically from the muscles, but adherent to many of them. In many places gray parts of the tumor projected through the capsule. Externally, the tumor seemed to be homogeneous with the consistency of soft cartilage, except dorsally, where there was a ridge of tough fibrous connective tissue from the humerus. None of the muscles originating on the humeral condyles and inserted in the forearm or hand had been invaded by the tumor. The synovial surface of the joint was smooth, glistening and yellowish gray, except for 22 by 12 mm in the capsule just ventral to the trochlear articular surface of the humerus, where it was occupied by a grayish nodular tumor tissue. Three hemorrhagic areas, from 2 to 5 mm in diameter, were within the grayish nodules replacing the synovia. The articular surfaces of the humerus, radius and ulna were all smooth, glistening, moist and of normal color.

The tumor was easily cut to a depth of 5 cm, when resistance was met. However, in places a small knife could readily be inserted entirely through the mass. The greater part of the growth lay ventral to the shaft of the humerus, which was markedly eroded and destroyed. On longitudinal section of the humerus and tumor (fig 4), more of the anterior than of the posterior half of the shaft was found to be destroyed, as only small spicules of bone from 1 to 2 mm in diameter remained over 6 cm of the former site of the anterior half of the shaft. In the posterior half, there was a similar gap of only 3 cm. In this region, adjoining the remaining fragments of intact bone, there were also eight or ten small irregularly circumscribed zones of hemorrhage from 2 to 5 mm in diameter.

The former marrow cavity was slightly bulged in the transverse diameter and free from bone over 8 cm proximal from the trochlea. It was filled with grayish tumor tissue similar to that found in the extramedullary part of the growth. Beginning 8 cm proximal from the trochlea and extending 31 mm more proximal, the marrow cavity was filled with delicate, interlacing bony trabeculae, mixed with grayish tumor tissue. Over this same length there was a subperiosteal bony thickening at the junction of the tumor with the intact shaft and on both surfaces of the bone exposed by longitudinal section. The maximum transverse diameter of this thickening was 5 mm, thus making the total transverse diameter of the bone 28 mm at a point 95 mm proximal to the upper trochlear border. In contrast, 25 cm more proximal, where the subperiosteal thickening was not present, the transverse diameter of the humerus was but 19 mm. This subperiosteal thickening was symmetrical on the two sides, white and of ivory appearance and consistency. At a point 105 mm proximal to the upper trochlear surface, there was an irregular transition between the mixed intramedullary bony trabeculation and tumor tissue to apparently normal bone marrow, which extended proximally 110 mm to the transverse surface of the bone made by amputation. The shaft of the bone over the latter extent was also apparently normal.

The extramedullary part of the tumor exposed by longitudinal section was completely surrounded by a white fibrous capsule of connective tissue, from the under surface of which from ten to twelve conspicuous and many more inconspicuous septums converged incompletely in the general direction of the center of the tumor mass, thus giving this mass the appearance of faint, irregular lobulation. These individual tumor units bulged slightly on this section. There was no gross bone or other differentiated tissue, save the previously mentioned radiating septums present on the background of the tumor in its extramedullary extent.

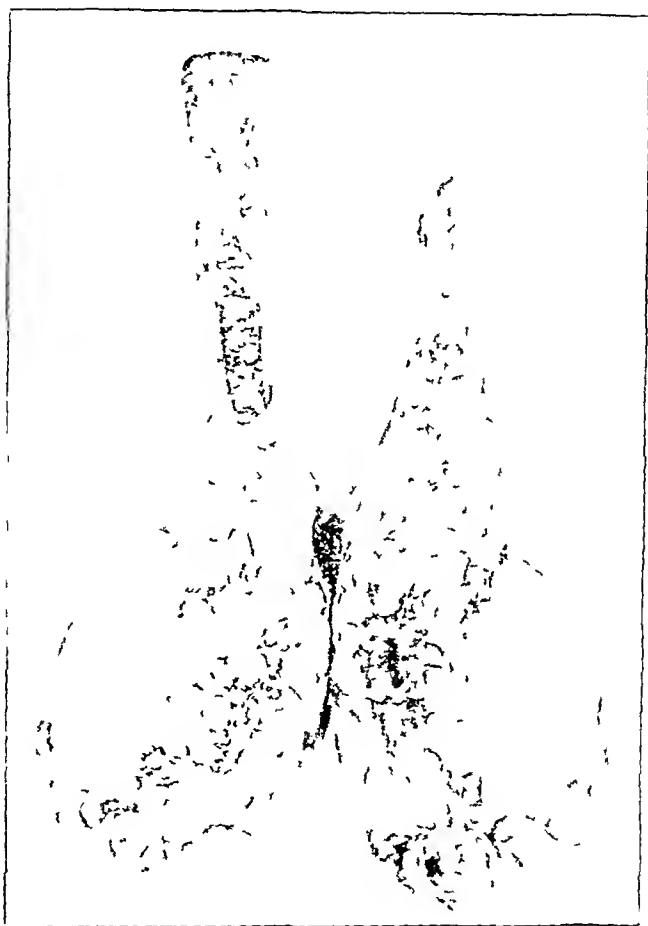


Fig. 4—Longitudinal section of the gross specimen of amputated humerus with tumor. The larger part of the tumor is seen to be anterior to the shaft of the bone.

Microscopic Examination—In sections of the curettage specimen removed from the arm in January and stained with hematoxylin and eosin, small irregular bits of tissue were composed largely of rounded or faintly polygonal cells, varying in diameter from 5 to 16 microns, the majority being from 9 to 12 microns. Two zones were seen within each of the irregular tissue units on the slide: a peripheral zone, composed largely of cells the nuclei of which were solidly hyperchromatic with rare mitotic figures; and a central zone, composed almost exclusively of cells slightly larger (averaging from 12 to 14 microns in diameter), the cyto-

plasm of which was frequently poorly fixed and thus ragged, but the nuclei of which were large and vesicular, with chromatin present in irregularly distributed hyperchromatic condensations (fig 5). The latter cells tended to be in linear configuration, one or two cells in width. From one eighth to one sixteenth of these nuclei contained mitotic figures. In well fixed cells of either class, the nongranular cytoplasm varied in width on either side of the nucleus from 2 to 8 microns, averaging in the majority from 2 to 3 microns in width. Thus, the cytoplasm made up about one third of the cell. Delicate, sparsely nucleated

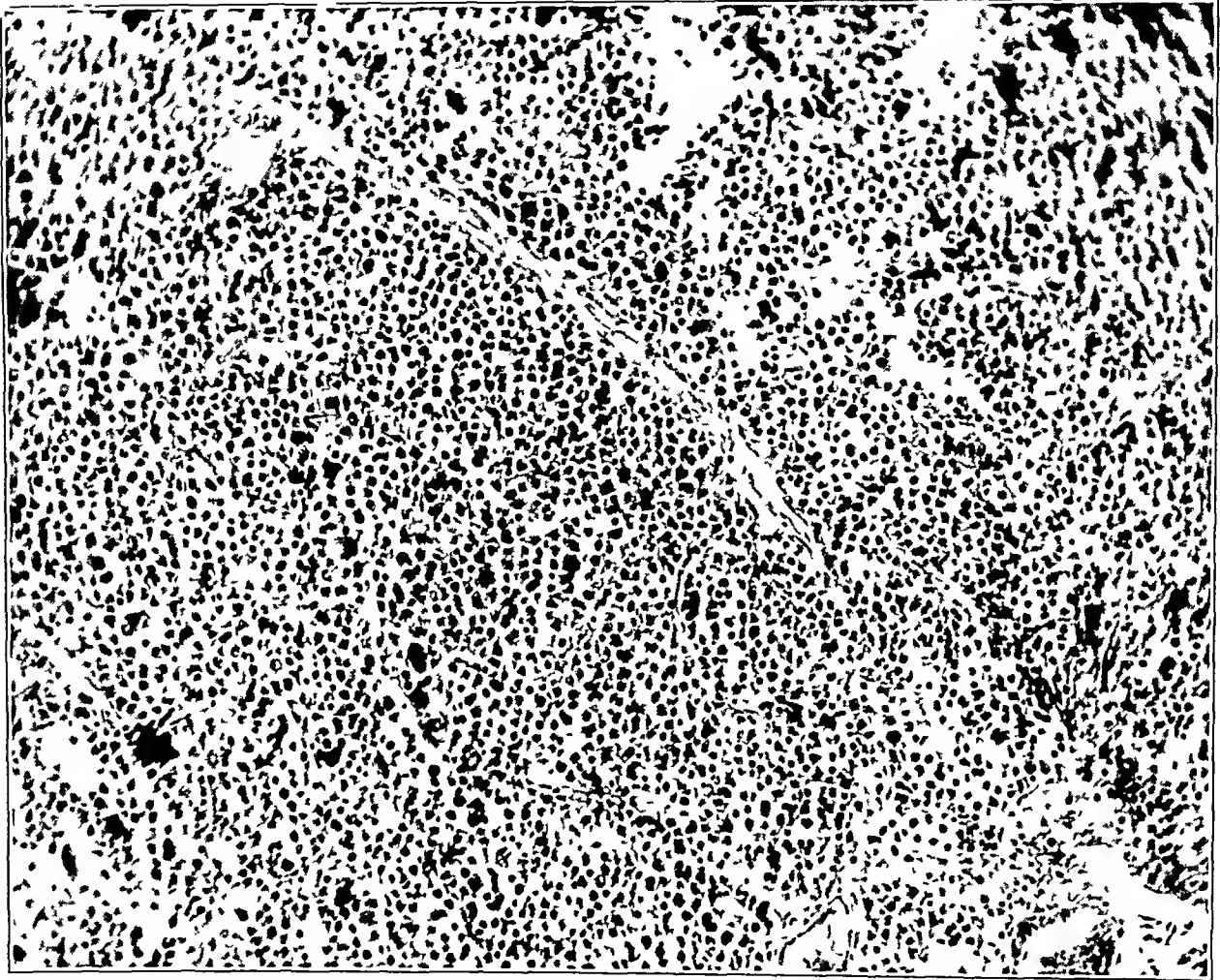


Fig 5—Photomicrograph of tissue removed at the second biopsy operation, done at about the same time as the roentgenogram in figure 3 was made, $\times 160$

stromal septums, from 8 to 30 microns in width, incompletely and irregularly divided the tissue into groups of from three to ten or twenty cells. Other wider, more cellular stromal units connected with smaller more regular fibrils. The nuclei of this heavier cellular stroma were sparse, but were composed about equally of small polygonal solid elements and of larger elongated paler elements, resembling but about twice the size of young fibroblasts. The last described stroma served as a matrix carrying the majority of the small blood vessels. The distance between

successive larger fibrils varied from 250 to 1,000 microns or more, while that between the smaller acellular fibrillae was from 30 to 100 microns. In sections stained with phosphotungstic acid and hematoxylin, the larger stromal septums were a deep homogeneous blue, while of the smaller fibrils, about half were bluish and the other half a golden yellow. Although this stroma was described in detail, it was but an inconspicuous part, composing 5 per cent or less of the total tissue, which, as a whole, gave the impression of a cellular mass. Disseminated throughout the entire tissue, in no obvious relation to the smaller cells, were other much larger cells, varying in diameter from 16 to 22 microns, containing two or three nuclei, and in rare instances, even four or five nuclei, which overlapped one another and were symmetrically placed within the cell. In these cells the cytoplasm was abundant, varying from 5 to 11 microns in width, averaging 7 or 8 microns. The nuclei of these cells were rounded or oval, and were a deeply stained homogeneous mass. Mitotic figures were rare in them, being observed in only one in a hundred such cells picked at random. These larger cells were present in a proportion of from one to twenty, to from one to forty or fifty of the previously described smaller cells. They were so strikingly similar to these smaller cells that they had the appearance of being but hypernucleated variants of the same origin. At many of the edges of macroscopic tissue units on the slides there was a cellular condensation, varying in width from 5 to 150 microns, in which the cells were flattened with nuclei all solidly hyperchromatic, and from two to four times as long as they were wide. Disseminated throughout the tissue were numerous small capillary and thin-walled blood vessels, moderately distended with erythrocytes, varying in number, with different zones, from one to two, and from two to six or eight per high power field of a diameter of 380 microns. Many smaller irregular zones of hemorrhage limited and intersected by tumor cells were seen, as well as many small zones of hemorrhage about the periphery of the macroscopic tissue units of these slides.

In sections taken from five different locations along the periphery and extending from 15 to 23 mm toward the center of the tumor, stained with hematoxylin and eosin, an identical picture was seen (fig 6), save for the quantity and quality of stromal tissue present. The essential features of these sections were equivalent to the previously described tissue taken at biopsy. Like those sections the tumor was seen to be composed largely of faintly polygonal, rounded and oval cells. Stroma was reduced to secondary prominence, although it was greater in abundance here than in the curettement specimen, since it was composed in this instance of from 5 to 20 per cent of the total area of these sections. In contrast to those sections, this tissue was more poorly vascularized. The occasional small blood vessels seen were devoid of erythrocytes.

Among cellular elements (fig 7), the essential and prominent part of the tumor, four types of cells were seen intermingled at random, save the first cell type to be described which was seen in greater abundance in close proximity to the larger fibrous stromal elements of the tumor. This cell resembled closely the small blood lymphocyte having a single, round, heavily stained nucleus, but with relatively more nongranular cytoplasm than that cell. Mitosis was never seen in this small cell the diameter of which measured in twenty specimens was almost constant at from 4 to 7 microns. Two other types which together made up about 80 per cent of the cells were practically identical save that one possessed a single large prominent nucleolus while its counterpart had no such discernible structure. These cells were large variable in size and were ovoid or polygonal, and mononucleated. They varied in size from 7 to 16 microns, many examples being found

of almost every dimension. Their cytoplasm was abundant and nongranular, making up from one fourth to one third of the total cell area. The nuclei were round or ovoid, varying in greatest diameter from 5 to 9 microns. Chromatin was present in hyperchromatic condensations, in the smaller cells of this class, making up three or four peripherally placed large blocks, and in the larger cells, six or eight smaller points, distributed somewhat more symmetrically within the nucleus. Mitosis was occasionally seen in these cells, but not with the frequency that it was observed in the same type of cell in the curettement specimen. Multi-

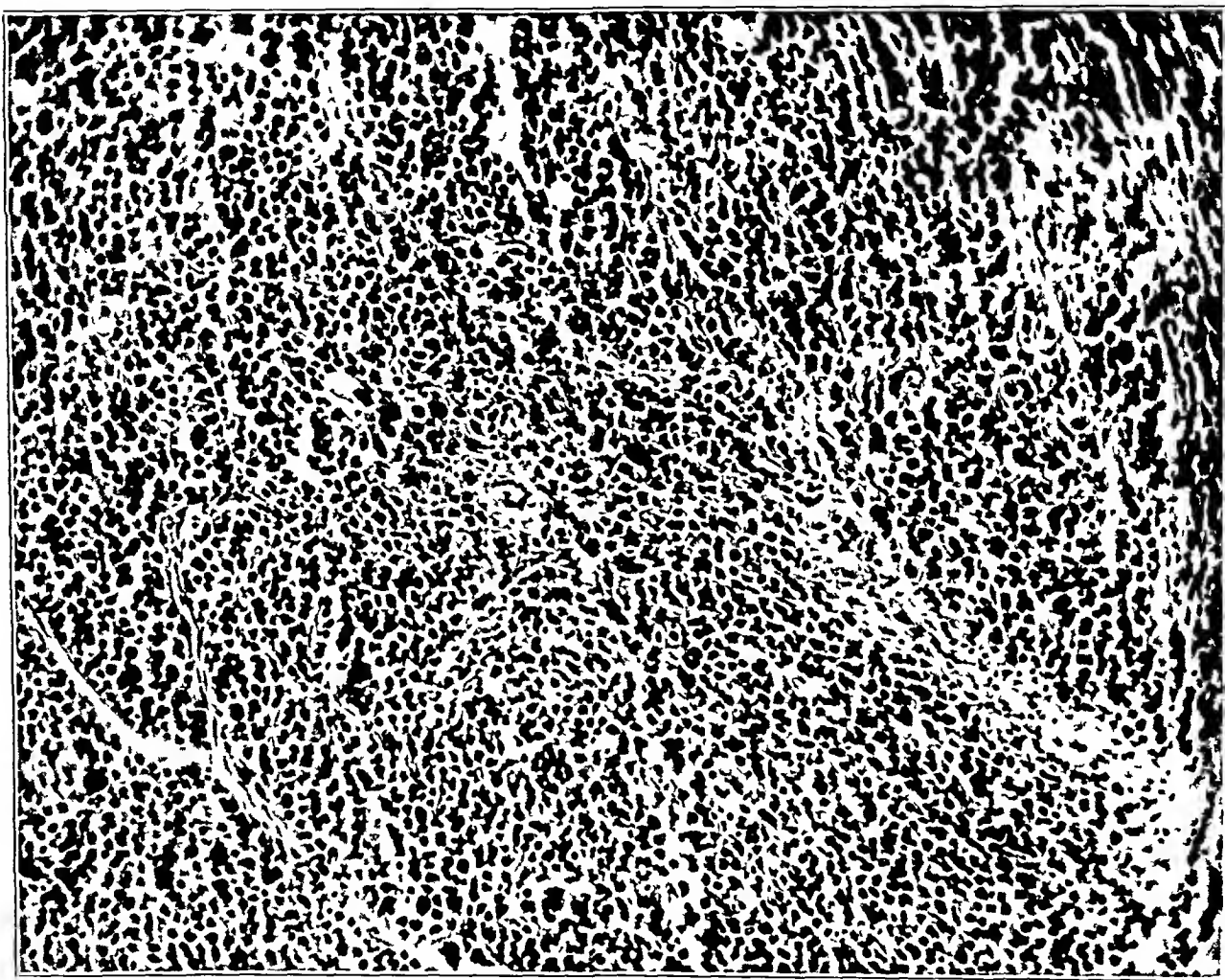


Fig 6—Photomicrograph of tissue from the periphery of the tumor taken from the gross specimen. The essentials of this picture are identical with figure 5, $\times 160$.

nucleated cells were present in greater abundance than in the previously described curettement specimens, varying from the proportion in which they were found there to one in ten cells in certain areas in these sections. They varied in size from 14 to 22 microns, many being 16 microns in diameter. As a rule, they contained from three to five nuclei but occasionally cells having from two to eight were seen. All of these nuclei were similar, being slightly ovoid, varying from 7 to 12 microns, with the majority 8 microns in greatest diameter, hyperchromatic,

and having multiple disseminated condensations of chromatin within the nucleus. Occasionally, mitosis could be seen in one of these extremely large cells, when they became especially hyperchromatic.

The stroma of the tumor in three of these sections was moderately prominent, making up from 10 to 20 per cent of the total area of the section. The relation of stroma and cellular zones of the tumor was not fixed, but varied markedly in different localities. Delicate white fibrous septums of connective tissue, with

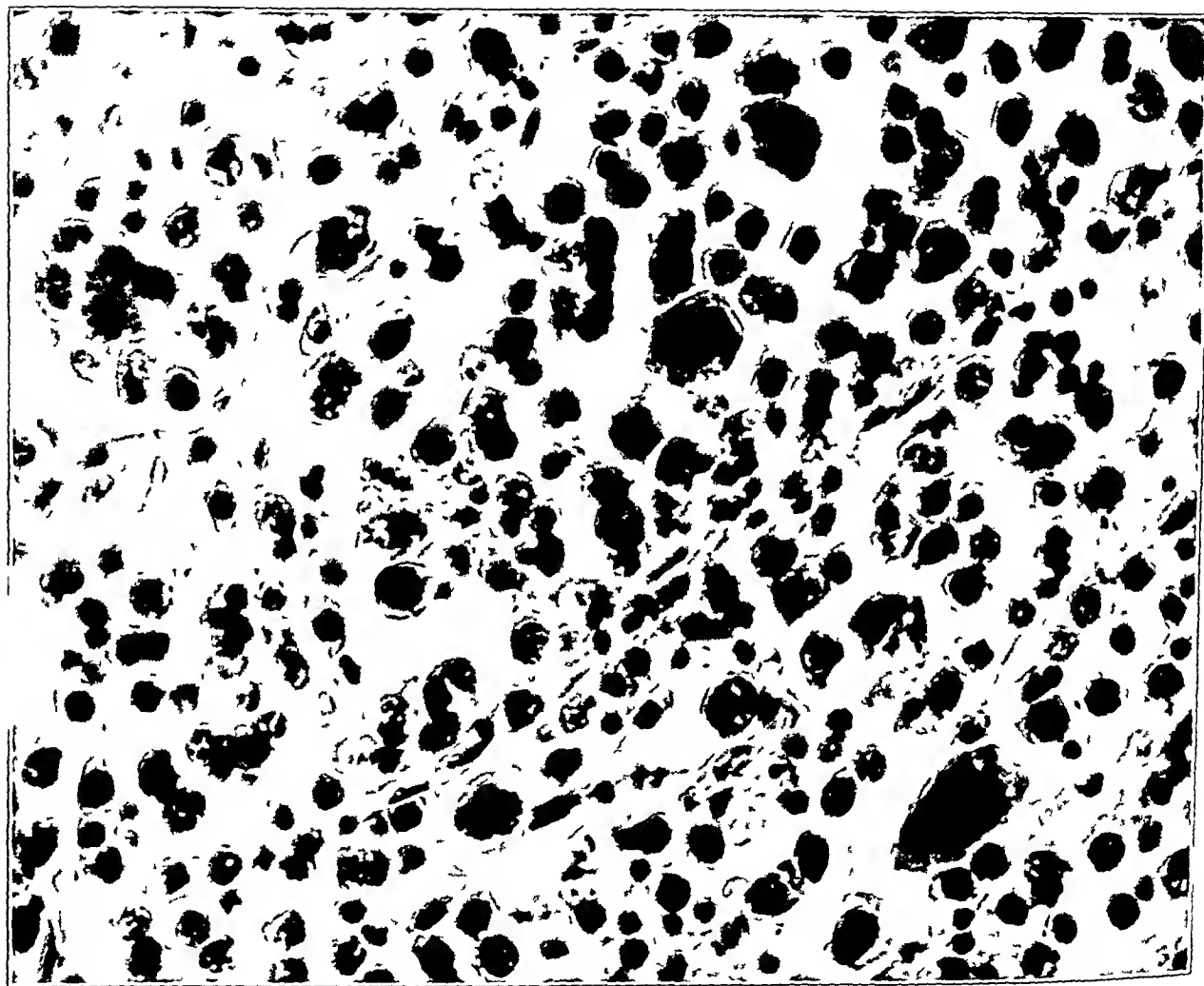


Fig 7—Photomicrograph showing types of cells to be found in this almost purely cellular tumor $\times 630$

occasional fibroblasts present irregularly and incompletely divided groups of from two to forty cells in width throughout the more cellular parts of the sections. Other wider stromal elements were present, of about half white fibrous connective tissue and the other half a more loose fibrillary structure, which, in sections stained with phosphotungstic acid and hematoxylin, gave the reaction of collagen. Fibroblasts and other irregularly heavily chromatinized cells, as well as cells that were definitely identical with the mononucleated cells of the cellular part of the tumor were present in moderate abundance trapped in the interstices.

of this stroma. In some localities the transition between stroma and cellular areas of the tumor was sharp, while in others stromal processes became more delicate and intermingled with narrow columns of tumor cells. Irregularly shaped deposits of calcium were seen within about one fourth or one third of the zones of such stromal tissue (fig 8). Tumor cells were never adjacent to the calcified areas, but definite noncalcified areas of the stroma were always interposed. In certain areas of stroma surrounded by fibrous connective tissue and in other localities set

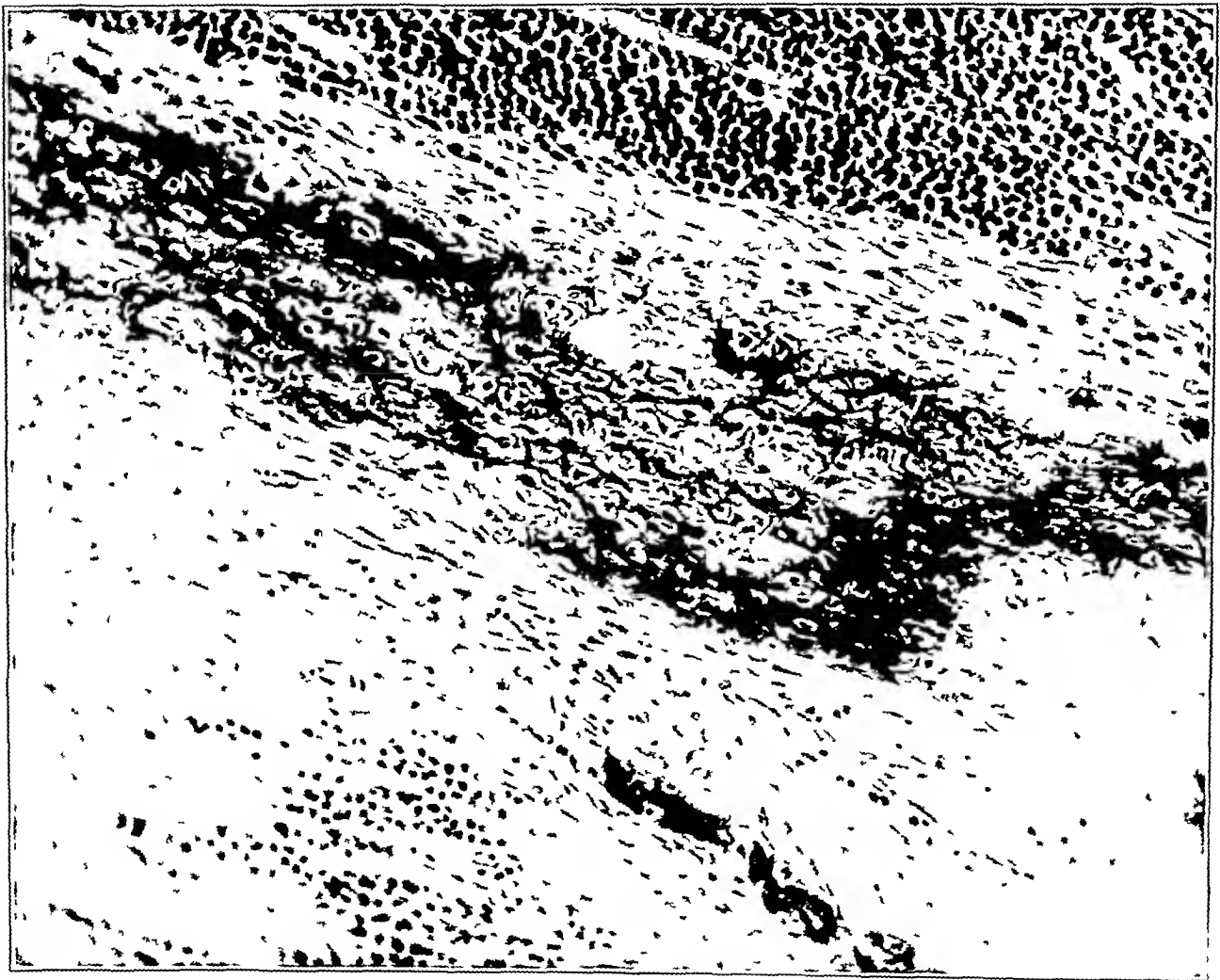


Fig 8—Photomicrograph showing partially calcified stroma to be found in the periphery of this tumor, $\times 160$

directly into an opening in the cellular part of the tumor there were linear hyaline structures having a fixed width of about 20 microns, with fine, wavy, longitudinal fibrillae and with flattened marginal nuclei resembling in size and location the nuclei of striated skeletal muscle (fig 9). All of the stromal elements described were not present simultaneously in two of the five sections, but various combinations of them were present in the other three slides. Thus this description is of the aggregate of stroma found in the peripheral 2 cm of the tumor. Every gradation might be found in an extensive study of these slides from a low power

field width composed almost exclusively of stroma to one exclusively cellular. A few blood vessels were to be found containing tumor cells in small numbers, admixed with erythrocytes. The capsule of the tumor was composed of a dense lamina of mature, white, fibrous connective tissue. Ten small, almost insignificant, spicules of lamellated bone were to be seen exclusively on one side of two sections. These represented the microscopic remnants of the destroyed shaft of the bone. These spicules differed from calcified stroma in that they were more

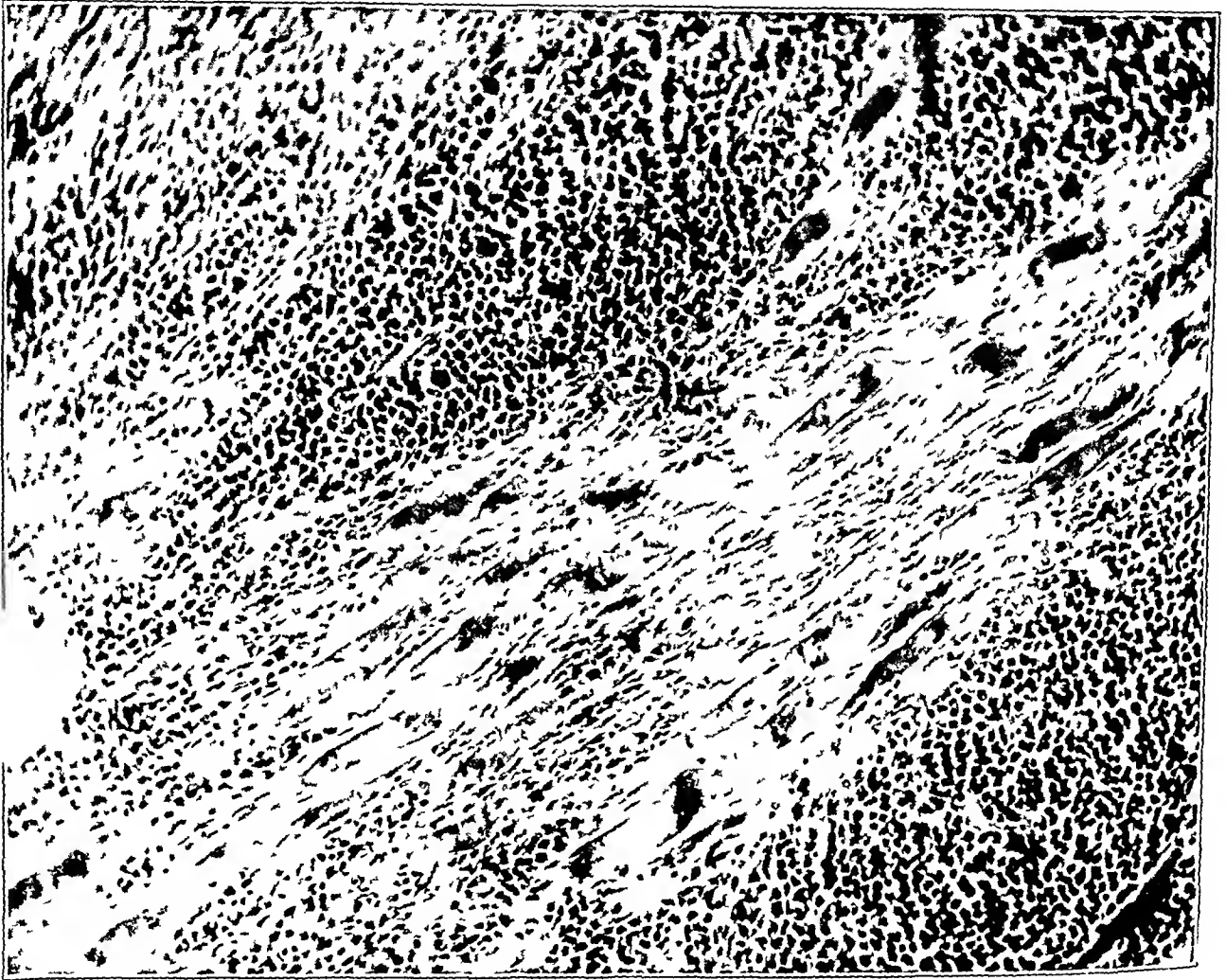


Fig 9—Photomicrograph showing hyaline substance probably partially degenerated skeletal muscle, included in the periphery of the tumor, $\times 160$

deeply stained with the purple-blue of hematoxylin, were trabeculated and were surrounded immediately by tumor cells some of which lay in definite small excavations analogous to the lacunae of Howship. There were no large multinucleated osteoclasts. As a rule the calcified stroma was not farther than 1 to 2 mm distant from these bony remnants all being from 25 to 30 mm beneath the tumor capsule. In a single section a definite wide band of stroma containing calcium deposits was seen 15 mm subcapsularly and 10 mm distant from the nearest spicule of lamellated bone.

COMMENT

According to the classification of the Sarcoma Registry of the American College of Surgeons, devised by Codman, Ewing and Bloodgood, malignant primary tumors of the bone include osteogenic sarcoma, multiple and solitary myeloma, angio-endothelioma and Ewing's sarcoma. A frequently found and confusing tumor is the benign giant cell tumor. Each type of this class of tumors has distinguishing characteristics.

The osteogenic sarcomas are osteoblastomas, that is, they arise from cells of the primitive mesoblast which are potential osteoblasts. Grossly, they originate in the metaphysis of the long bones, with frequently the clinical triad of trauma, tumor and pain. It is usually a disease of the young, the incidence peak falling in the second decade.^{*} However, no age group is free from the disease. Mirroring the age of the patient, and thus skeletal growth energy, are the gross anatomic types, the osteogenic and the osteolytic varieties of osteogenic sarcoma. Kolodny pointed out the fact, supported by the data of the Sarcoma Registry, that osteolytic tumors are more frequent in adults than in young persons. Grossly, and thus also roentgenologically, there are frequently seen beneath the raised periosteum calcified spicules arranged perpendicular to the long axis of the bone, in the characteristic "sun-ray" configuration. This is not an essential sign in osteogenic sarcoma, being conspicuously absent in the osteolytic varieties found more commonly in adults. Lipping of the periosteum by new bone formation at the junction of the tumor and intact shaft, the so-called "reactive triangle," is thought by Codman and other authorities to be an essential and cardinal sign of osteogenic sarcoma. The consistency of the tumor varies greatly, every gradation being seen, from the osteogenic types as seen in the sclerosing variety to the purely cellular osteolytic types. However, even in an extreme osteolytic osteogenic sarcoma there is said to be always a tendency toward bone formation, showing as a few scattered sometimes microscopic, foci of new bone at some place in the tumor proper. The microscopic picture is varied, depending on the degree of differentiation of these descendants of the primitive osteoblast and the quality and quantity of intercellular substance. Kolodny dogmatically stated that "osteogenic sarcomata are never of the round cell type. If the leading cell of the tumor is a round cell it is not an osteogenic sarcoma." Other authors (Codman, Ewing, and Simon²³) are less insistent on this point.

Multiple myelomas comprise a characteristic clinical and pathologic group, occurring in contrast to osteogenic sarcoma, largely in persons between the ages of 40 and 70 years, with the peak of incidence in the

²³ Simon, W. V. Die Knochensarcome. *Ergebn. d. Chir. u. Orthop.* **16**: 364, 1923.

sixth decade Multiple distribution of tumors involving especially the short flat bones, as the ribs, sternum, clavicle, vertebrae and cranium, with slowly progressive anemia and cachexia punctuated by multiple and recurrent pathologic fractures, are the outstanding features of the disease The roentgen rays show the tumor in the characteristic locations as rounded, punched-out areas or as a diffuse rarefaction of bone producing a mottled effect Bence-Jones protein is present in the urine of many of these patients, but a similar proteosuria is associated with other tumors of the marrow cavity, notably metastatic carcinoma and endothelioma Grossly, an outer table of parchment-like thinness is found in the affected bones, covering a dark red or gray gelatinous, freely bleeding tumor The histology of multiple myeloma is typical The tumors are composed of rounded or oval cells usually with a single rounded nucleus and a scanty reticular stroma Hypernucleated tumor giant cells with two to four nuclei are commonly seen The cells in the majority of cases have been identified with plasma cells, although Geschickter and Copeland¹⁴ stated that such cells do not take the characteristic plasma cell stain by the Unna-Pappenheim or polychrome methylene blue technics, and that such cells lack the perinuclear halo In contrast, Versé,¹⁵ relied on such positive signs in identifying his cases of multiple plasmocytomas Although less frequent, certain multiple tumors are said (Kolodny, Ewing²⁴) to be composed of cells resembling myeloblasts, lymphocytes and megaloblasts Some formation of new bone and stroma occurs, as attested by the healing of pathologic fractures and by microscopic examination Solitary myelomas, that is, tumors identical with the multiple tumors just described, but originating from a single focus, have not been found with frequency

Angio-endothelioma, a rare tumor, is similar in its clinical aspects to osteogenic sarcoma Its only distinction is a histologic one, cells being arranged in alveoli and tubules, traceable in some part of the tumor to proliferation of vascular endothelium It is safe to say that such malignant tumors of the bone are correctly diagnosed only at autopsy, since in the reported cases various diversified types of osteogenic sarcoma have been approximated clinically and roentgenologically The possibility of metastatic carcinoma should always be deposed

Ewing's sarcoma, although described by Ewing²⁵ himself as a diffuse osteolytic endothelial myeloma of the bone, has most recently been considered by Copeland and Geschickter²⁶ as a primary sarcoma of the bone originating either in the haversian systems or in some other

24 Ewing J. *Neoplastic Disease* ed 3 Philadelphia, W B Saunders Company 1928

25 Ewing (footnote 1 reference 1)

26 Copeland and Geschickter (footnote 1 third and fourth reference)

subperiosteal location. The group is considered as a highly homogeneous entity, characterized by recurrent attacks of pain occurring in a person practically always between the ages of 5 and 25 years, subsequently followed by tumor, which roentgenologically is seen to be a thickening of the shaft of the long bones in longitudinally concentric layers, later accompanied by widening and mottling of the marrow cavity due to internal bony destruction. The rarity of pathologic fracture, the exquisite sensitiveness of the tumors to roentgen therapy and the marked early tendency of the tumor to metastasize to other bones are further striking peculiarities of this tumor. Fever is commonly present in patients with Ewing's sarcoma in all stages. The soft parts of the tumors are firm and of a grayish white and divided into lobules by a number of radiating connective tissue strands. Microscopically, small, rather uniform polyhedral cells with scanty cytoplasm and rounded or oval nuclei make up the tumor. Multinucleated tumor cells are conspicuously absent. Fibrous trabeculation with hyaline-like intercellular substance divides the tumor tissue frequently to resemble an alveolar arrangement. So frequently are biopsy specimens diagnosed as inflammation of the bone that such a report alone should make one suspect this condition. Bence-Jones protein has never been found in the urine of these patients.

The benign giant cell tumor and allied conditions characterized by the presence of giant cell osteoclasts have recently been subjected to a thorough-going critical analysis by Geschickter and Copeland,²⁷ in which the relationship of these giant cell tumors as a progressing stage of the same type of lesion as osteitis fibrosa, a fact many times previously suspected, is reemphasized with new data. The tumor occurs largely in young adults, the peak incidence falling in the third decade, an age slightly beyond the average for osteogenic sarcoma and Ewing's tumor, although not an inconspicuous number of giant cell tumors occur in adults of all ages up to 50 or 55 years. The sites of bony involvement are the usual points of trauma to the skeleton—about the knees and shoulders and in the region of the trochanters and the distal part of the radius. The small bones of the extremities are occasionally involved, while in osteogenic sarcoma such a location is almost never seen. The tumor enlarges by central destruction with peripheral expansion and subperiosteal bony proliferation. The picture at any single moment depends on the relative preponderance of these two processes. Metastases are never observed in well scrutinized cases. Roentgenologically, an expanded marrow cavity is seen, usually with an intact thin bony shell about the periphery of the tumor. Internal bony trabeculation almost

27 Geschickter, C. F., and Copeland, M. M. Osteitis Fibrosa and Giant Cell Tumor, *Arch. Surg.* **19** 169 (Aug.) 1929 footnote 5.

universally present, is responsible for an appearance resembling soap bubbles. The solid portions of the giant cell tumors are friable and crumbly, thus pathologic fracture is common in this condition. The soft parts of the tumor within the cystic portions are soft, red and profusely bleeding when disturbed, thus having been likened to currant jelly. In the healing varieties, fibrous connective tissue and dense peripheral bone may predominate. The microscopic structure of the tumor has a single fixed characteristic giant cells of the osteoclast type, which should be carefully contrasted with foreign body giant cells (Langhans) and tumor giant cells of other conditions. Numerous blood vessels are embedded in a stroma of elongated round or polygonal cells with large pale nuclei. Stromal cells are but slightly pleomorphic. In certain areas of many giant cell tumors can be found zones devoid of giant cells and poor in stroma and blood vessels, composed almost exclusively of rounded cells, zones that are similar histologically to myelomas, except that tumor giant cells are absent. The latter, however, are said to be absent in some varieties of myelomas. Clinically, with the slow but frequently progressive course, together with characteristic roentgenograms, the diagnosis of giant cell tumor is easily made in certain instances.

Atypical and borderline cases of malignant tumors of the bone are difficult to assign to one of the previously described categories. Frequently, the diagnosis can be made easier by the roentgenologist than by the pathologist. Particularly is this true of the cellular osteogenic sarcomas and of biopsy specimens taken by unfortunate chance from atypical zones of tumors elsewhere orthodox. In attempting to classify any tumor of the bone, data must be compiled from three sources: clinical, roentgenologic and pathologic, both gross and microscopic. The last item is a factor of marked variability among the osteogenic sarcomas. When, as in the present instance, a single of these aids is misleading, the clinical and gross pathologic data will furnish the most valuable clues to the origin and relations of the tumor. Roentgenography, as dependent on gross anatomy, frequently accurately supplants the latter in the living patient. From a consideration of the foregoing descriptions, the tumor in our case could have been either a cellular osteogenic sarcoma or a solitary myeloma. The sudden onset and development of the tumor in our patient, its location in the distal part of the humerus, the age of the patient and gross and microscopic pathologic changes all conclusively demonstrated that the tumor could not be a giant cell tumor. Likewise it was highly improbable that our patient had Ewing's sarcoma because of her age, the absolute dissimilarity in location of the tumor and its mode of growth and the gross and microscopic anatomy of the specimen.

The history of trauma, followed later by pain and tumor are characteristics that are shared by numerous tumors of the bone. Myeloma is usually a tumor with silent onset. However, the cases of solitary myeloma found in the literature prominently display trauma as a factor in the presumptive etiology of the condition. The relation of trauma to causation in this as in other tumors is not clear. The age of our patient (65 years) favored a diagnosis of myeloma although it is not utterly inconsistent with osteogenic sarcoma. The subnormal temperature (averaging about 97 F) during the time prior to amputation, with a rise of the temperature to a more normal range of 98 to 98.6 F following amputation is suggestive of myeloma being not infrequently observed in multiple instances of that condition. The occurrence of cells in the blood, designated as "transitional cells," in one instance to the extent of 6 per cent and in another to the extent of 18 per cent is of interest. The lack of a definite description of these cells precludes the possibility of determining their relationship to the condition. Localization of the tumor in the distal third of the humerus is evidence against osteogenic sarcoma, according to certain authors. Kolodny stated that "an osteogenic sarcoma below the deltoid tubercle is a curiosity." However the metaphyseal situation is suggestive of this condition. The gross appearance of the tumor was similar to the bone destructive variants of osteogenic sarcoma, definitely known to be more frequently seen in adults than in the young. Periosteal lifting at the junction of tumor with the intact shaft was present in this case. This single configuration is said to be pathognomonic of osteogenic sarcoma.

Microscopic analysis of the tumor leaves much to be desired as to the conclusiveness of an opinion, rendered from this source, as to the origin of the tumor. At first impression of a single section one was struck with the similarity to the microscopic picture of myeloma. However the type could not be that of the most common of the myelomas the plasma cell type, since, although a few cells having the typical appearance of plasma cells were seen with eccentric peripherally chromatinized nuclei, the majority of the nuclei were more pale, vesicular and placed symmetrically. Wallgren¹⁷ and Christian²⁸ stated that the myeloma cell is a transitional form not to be classified as either a plasma cell or a myelocyte. The cellular zones of the tumor in our case, which in the aggregate, composed from 90 to 95 per cent of the growth had as a striking feature a moderate admixture of tumor giant cells a characteristic frequently shared alike by osteogenic sarcomas and myelomas.

28. Christian H. A. Multiple Myeloma. A Histological Comparison of Six Cases. *J. Exper. Med.* 9:325, 1907.

The usual cellular osteogenic sarcoma is said to demonstrate a greater prominence of the spindle-shaped tumor cell rather than the retting rôle that this type of cell played in this instance. On further search through more sections, a not inconspicuous fibrous and collagenous stroma was found, which in places was irregularly calcified, apparently arising as a product of cells morphologically similar to cells found in the purely cellular parts of the growth. This fact would tend to influence an assumption that the progenitors of osteoblasts had a rôle in the proliferation of this tumor. In sections of typical myeloma, no such intercellular substance is seen. These observations prove the thesis that a single biopsy specimen or a single microscopic sample of a malignant primary tumor of bone may be misleading. The microscopic analysis of a tumor of the bone is never complete until a composite of microscopic observations is synthesized into a single description.

The evidence (fig 1 *A* and *B*) that a benign cystic lesion of the humerus was present prior to the onset of the tumor we believe to be definite. It is impossible to estimate accurately the actual duration of this condition, but, using symptoms of pain as an index, we believe that it must have been present for at least one year prior to the first fracture. In the roentgenogram (fig 1 *B*), taken at the time of the second fracture, evidence is present in the slightly circumscribed elevation of the periosteum that is not inconsistent with the presence of a malignant tumor. Thus the results of biopsy at this time were probably misleading as by chance bone was taken that was not in contiguity with the suspicious raised periosteal zone. Microscopic preparations made from this material showed no definite alterations that would predict the condition soon to be obviously present. However, cartilage was seen in these sections (fig 2). The relationship of this cartilage to the subsequent almost purely cellular tumor is not clear. We believe that the definite change in the patient's symptoms which followed a few days after the third pathologic fracture is significant. This was the symptomatic onset of sarcoma. The roentgenogram (fig 3) taken during the following week showed unquestionably that a malignant tumor was present. The actual onset of this condition we would place a few weeks prior to the second pathologic fracture. If reasoning on this evidence is valid, sarcoma was present about three months before enough clinical and roentgenologic data were adduced to demonstrate this fact conclusively.

SUMMARY

On the positive evidence of bony periosteal lifting and the presence of a significant although small amount of stroma that could have been produced by potential osteoblasts the diagnosis of an osteolytic myelogenous sarcoma is based. The age of the patient and the location in the

distal metaphysis of the humerus are rare qualities associated with this type of neoplasm. The majority of microscopic fields of sections of this tumor demonstrate a picture not inconsistent with myeloma, thus illustrating the deceptiveness of an incomplete histologic study of a malignant tumor of bone. We consider our case as an instance of a malignant neoplasm complicating cystic disease of the bone.

THE PRODUCTION OF HYPERPLASIA OF THE THYROID GLAND BY CHEMICAL MEANS

WITH SPECIAL REFERENCE TO PURINE BASES AND THEIR DERIVATIVES *

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AND

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In previous publications,¹ we have called attention to the hyperplasia, desquamation and loss of colloid that occur in the thyroid gland during the course of systemic infections and toxemias. This triad of changes in the thyroid gland seems clearly to be due to a demand for excessive function of the thyroid cells as a result of chemical or physiologic stimulation. It is secondary rather than primary, since the cellular changes obtained were brought about without any possibility of a direct local action of the bacteria on the thyroid cells. This explanation also adequately accounts for the loss of colloid and iodine in the gland. If it is assumed that the process is best explained on a chemical basis, one's attention is offhand directed toward the by-products of protein catabolism, since so many of them are known to be toxic, and because many of the bacterial toxins themselves are proteins.

Vaughan² held that the proteins of bacteria are best classified as nucleoproteins. He stated further that "all true proteins contain a poisonous group," and that this is liberated when the protein molecule is stripped. When faced with the fact that the splitting of proteins by enzymes or other chemical means may involve the liberation of vast

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* From the Department of Surgery, Washington University School of Medicine.

Read at the Annual Meeting of the American Association for the Study of Goitre, Seattle, July, 1930.

1 Cole, W. H. and Womack, N. A. Reaction of the Thyroid Gland to Infections in Other Parts of the Body, *J. A. M. A.* **92**: 453 (Feb. 9) 1929. Cole, W. H., Womack, N. A. and Gray, S. H. The Thyroid in Infections and Toxemias. Pathological Changes in the Human Gland. *Am. J. Surg.* **6**: 221, 1929. Womack, N. A., Cole, W. H., and Heideman, A. G. The Thyroid Gland in Infections. The Effect Upon the Basal Metabolic Rate. *Endocrinology* **12**: 773, 1928.

2 Vaughan, V. C., Vaughan, V. C. Jr., and Walter, J. Protein Split Products in Relation to Immunity and Disease. Philadelphia: Lea & Febiger, 1913, p. 18.

numbers of poisonous groups, we marvel at the manner in which the human body combats them and prevents their absorption. Some of these poisons need not be present in very large amounts to produce symptoms. A statement made by Kendall³ seems significant in this respect, viz. "The aromatic amines produced from the amino-acids—tyramine, phenylethylamine, beta-imidazolethylamine and indolethylamine—are physiologically active, even in very small amounts." We were also encouraged to investigate the by-products of protein catabolism, because the organisms that produced the most changes in the thyroid gland belonged to the group inhabiting the intestinal tract and possessing proteolytic and putrefactive qualities. It should be noted, also, that practically all the products of protein catabolism may be produced in the body by the enzymatic action of the secretions of the various organs on the proteins of bacteria or of the body tissues. For this reason, we have investigated the effect on the thyroid gland of the administration of some of the products of nucleoprotein catabolism. Of the constituents of nucleoproteins, the purine bases were chosen for experimental purposes because they seemed, perhaps, to offer the greatest possibility of toxicity to the thyroid gland. Furthermore, the purine bases (adenine and guanine) are much more readily detached from the nucleoprotein molecule than the pyrimidine bases (cytosine and thymine). However, the exact derivative responsible for any toxic effect that might be produced by the purine bases would be difficult to determine, because, as Jones⁴ remarked, "In the organism the purine groups of nucleic acid readily undergo deamination with the final formation of the oxypurines, xanthine and hypoxanthine, and this is the case whether the nucleic acid originates from the food, from metabolism of the cell nucleus or from the bodies of dead leucocytes."

There can be no doubt that a close relationship exists between the thyroid secretion and the catabolism of proteins. Mathews⁵ stated "The great and predominant factor in the catabolism of protein is the internal secretion of the thyroid gland, thyroxin. This holds toward protein metabolism a position somewhat similar to that held by insulin in carbohydrate metabolism. Thyroxin hastens the oxidation of protein, and perhaps of other materials as well."

Histamine was the first chemical that we used in attempting to produce pathologic changes in the thyroid gland, since it is known to be formed in the body as a product of protein catabolism. Since the thy-

3 Kendall, A. I. *Bacteriology*. Philadelphia, Lea & Febiger, 1928.

4 Jones, Walter. *Nucleic Acids*. New York, Longmans, Green & Company, 1914.

5 Mathews, A. P. *Physiological Chemistry*. New York, William Wood & Company, 1925.

roid gland of the dog seems more susceptible to changes than that of other animals, we used dogs, for the most part, throughout. We found a definite desquamation with loss of colloid and beginning hyperplasia in the thyroid gland in two dogs in spite of the fact that the dosage given over the period of three days was insufficient to produce toxic symptoms of marked significance (fig 1)

However, mindful of the possibility that the products of catabolism of nucleoproteins might be involved in the production of the changes in

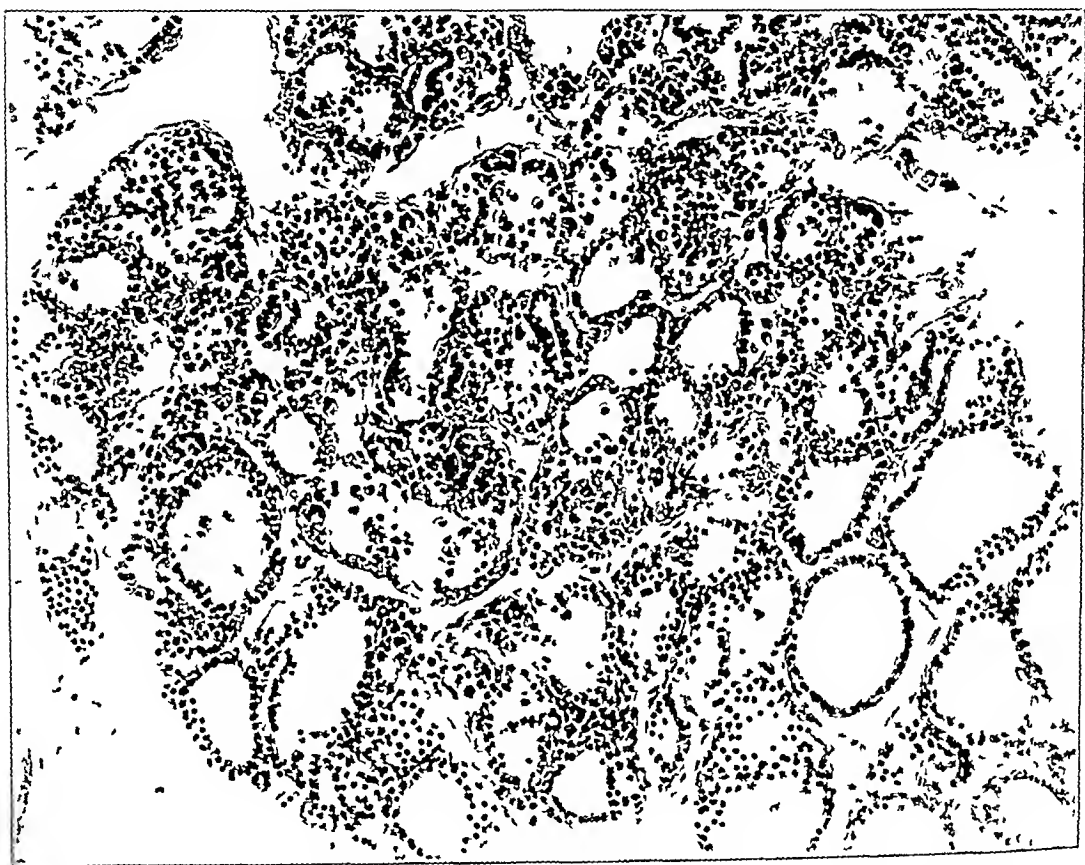


Fig 1—This section represents the thyroid gland of a dog which had received 133 mg of histamine subcutaneously, divided into four daily doses. The animal exhibited signs of toxicity and was killed on the day following the last dose of histamine. The section was removed immediately after death. A loss of colloid, with desquamation of thyroid cells, and early hyperplasia can be made out. A small section of the thyroid gland was removed before administration of the histamine, and the gland was found to be normal in appearance.

the thyroid gland following systemic infections, we chose to investigate the purine bases and their derivatives. The purine bases themselves are expensive and difficult to obtain. With a small amount of xanthine (2-6 dioxy purine) available an injection was made into one animal (dog). A definite desquamation of epithelial cells and loss of colloid

with beginning hyperplasia were found even though the dose was insufficient to produce symptoms (fig 2). On one occasion, we administered guanine, orally, but found no changes in the thyroid gland of the animal when it was examined post mortem a day or so later. The fact that the guanine was given by mouth and the xanthine intravenously may explain the impotency of the guanine. Although xanthine is not a direct component of the nucleic acids both hypoxanthine and xanthine as previously stated, are formed in the body during the catabolism

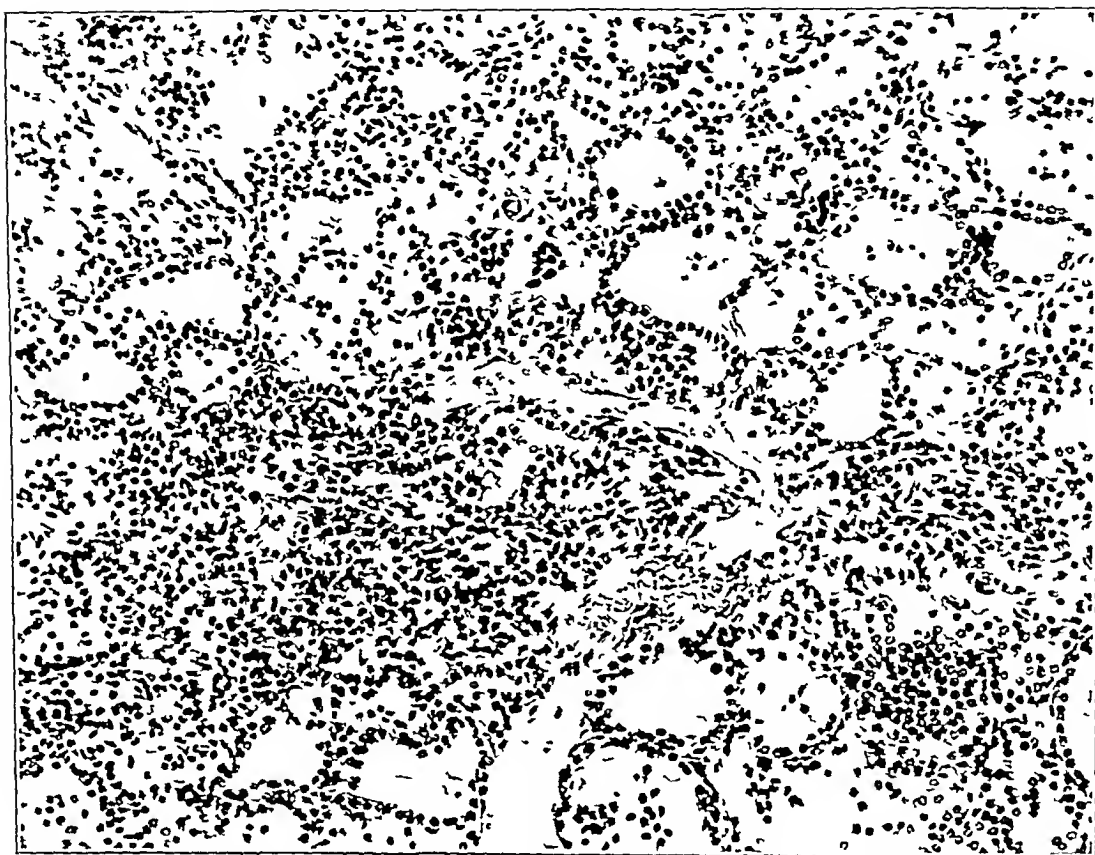


Fig 2—This section is from an animal that received 1 Gm of xanthine (with the addition of a small amount of alkali to increase the solubility) intravenously in divided doses over a period of three days. No toxic symptoms were noted, but the animal was killed on the day after the last dose was given, and a section of the thyroid gland was removed immediately after death. Note the loss of colloid, the decrease in size of acini and the desquamation of acinous cells with early hyperplasia. It is significant that these changes were most pronounced at the periphery of the gland whereas the central part revealed little change. A small piece of the thyroid gland was removed before administration of the xanthine, and the gland was found to be normal in appearance.

of nucleic acids by hydrolysis of adenine and guanine respectively. Hypoxanthine is readily oxidized in the body to xanthine. By further oxidation in the presence of xanthine oxidase, an enzyme that is present in the human body only in the liver, the xanthine may be converted into

uric acid To the present time we have been unable to produce any changes in the thyroid glands of dogs by administration of uric acid even in such huge doses as from 1 to 3 Gm per kilogram Since xanthine and some of its methylated derivatives (see following paragraph), when administered to animals do produce changes in the thyroid gland, it would appear that the intermediary products of the catabolism of proteins especially the nucleoproteins, may be responsible for some or all of the deleterious effects observed

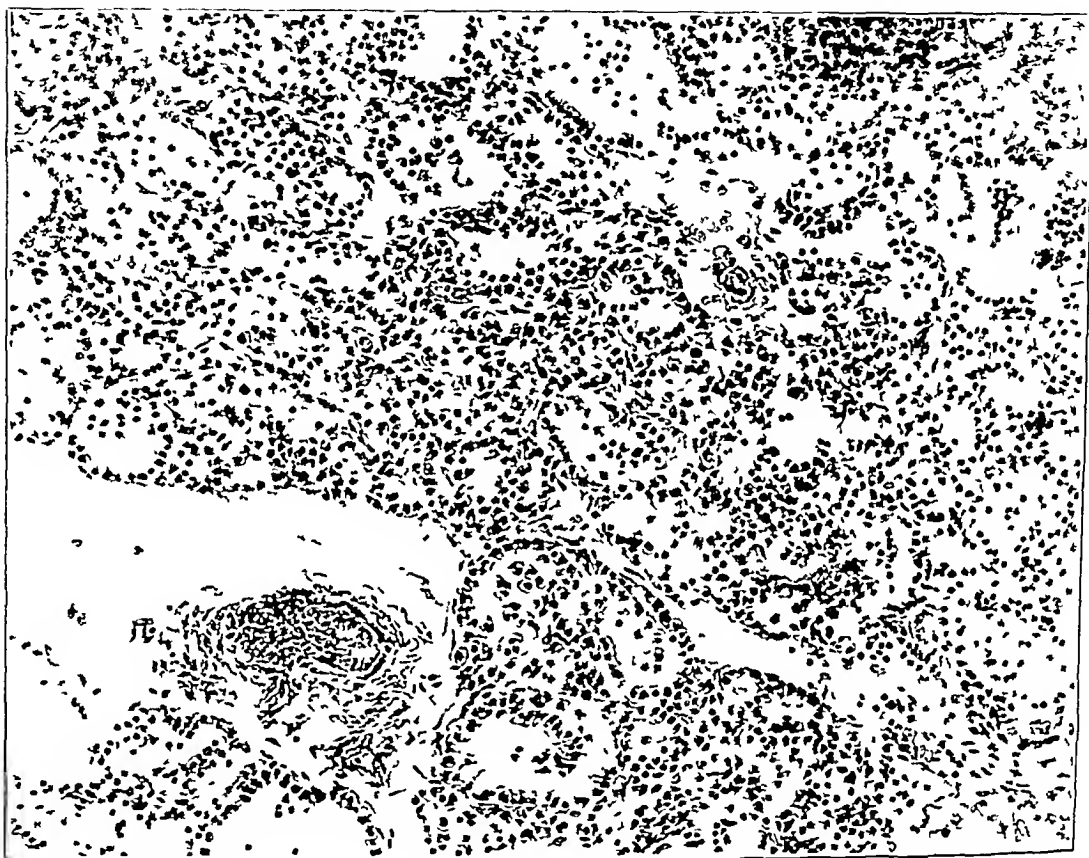


Fig 3—This section of thyroid gland was removed from an animal which died twenty-four hours after ingestion of 0.15 Gm of caffeine per kilogram of body weight A section removed a few days previously was normal in appearance This illustrates how rapidly the colloid may be depleted and other changes, including desquamation and early hyperplasia, take place

The methylated derivatives, caffeine (1-3-7 trimethyl-xanthine), theophylline (1-3 dimethyl-xanthine) and theobromine (3-7 dimethyl-xanthine) were used When given to the point of toxicity, each produced desquamation, loss of colloid and beginning hyperplasia of the thyroid gland in dogs in practically every instance (figs 3, 4, 5 and 7) Occasionally, the hyperplasia was so marked that the sections could

scarcely be differentiated from those seen in exophthalmic goiter of human beings

In 1917, Means, Aub and DuBois⁶ observed that when caffeine was administered to human beings in doses varying between 0.5 and 0.65 Gm., there was a constant rise in the basal metabolic rate varying between 7 and 23 per cent. The tendency for the methylated purines (including caffeine) to produce hyperplastic changes in the thyroid gland, as we have noted, may possibly explain this rise in the basal

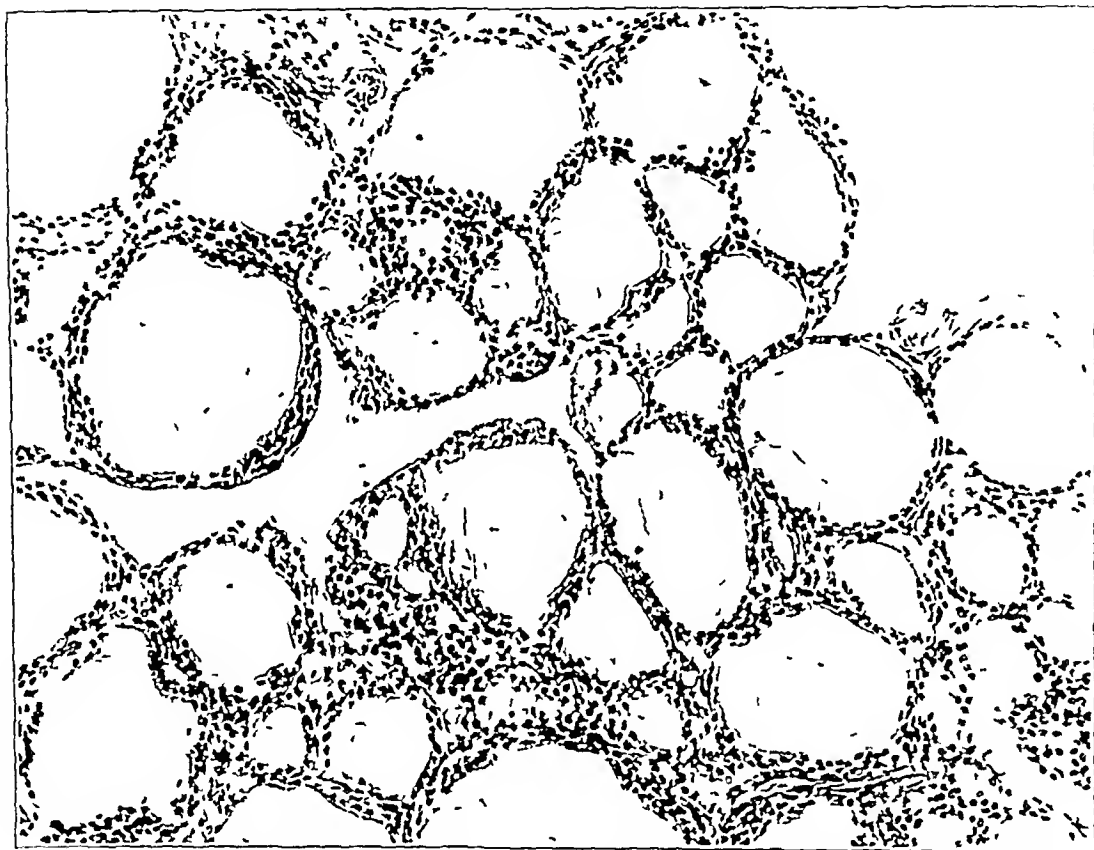


Fig. 4—Section from a normal thyroid gland of a dog previous to experimentation. Note large acini (see fig. 5)

metabolic rate as a stimulative action of the caffeine on the thyroid gland and allied organs. Further support is lent to this theory by the remarks of Crile⁷ who has been a strong advocate of the theory that practically all the 'stepping up' processes observed in the human being are expressions of hyperthyroidism.

6 Means, I. H., Aub, I. C. and DuBois, E. F. Clinical Colorimetry. The Effect of Caffeine on the Heat Production. *Arch. Int. Med.* 19: 832 (May) 1917.

7 Crile, G. W. Thyroidectomy. Indications, Methods, Complications and End Results. Lecture delivered before the St. Louis Clinics. St. Louis, June 20, 1930.

Since the three methylated purine bases (caffeine, theophylline and theobromine) produce such striking changes in the thyroid gland,⁸ when given to dogs in toxic doses, the possibility suggests itself that there may be other methylated compounds of similar nature in the organism, occurring in excess or abnormally during the destruction of protein. Although the better known of the methylpurines found in the human urine

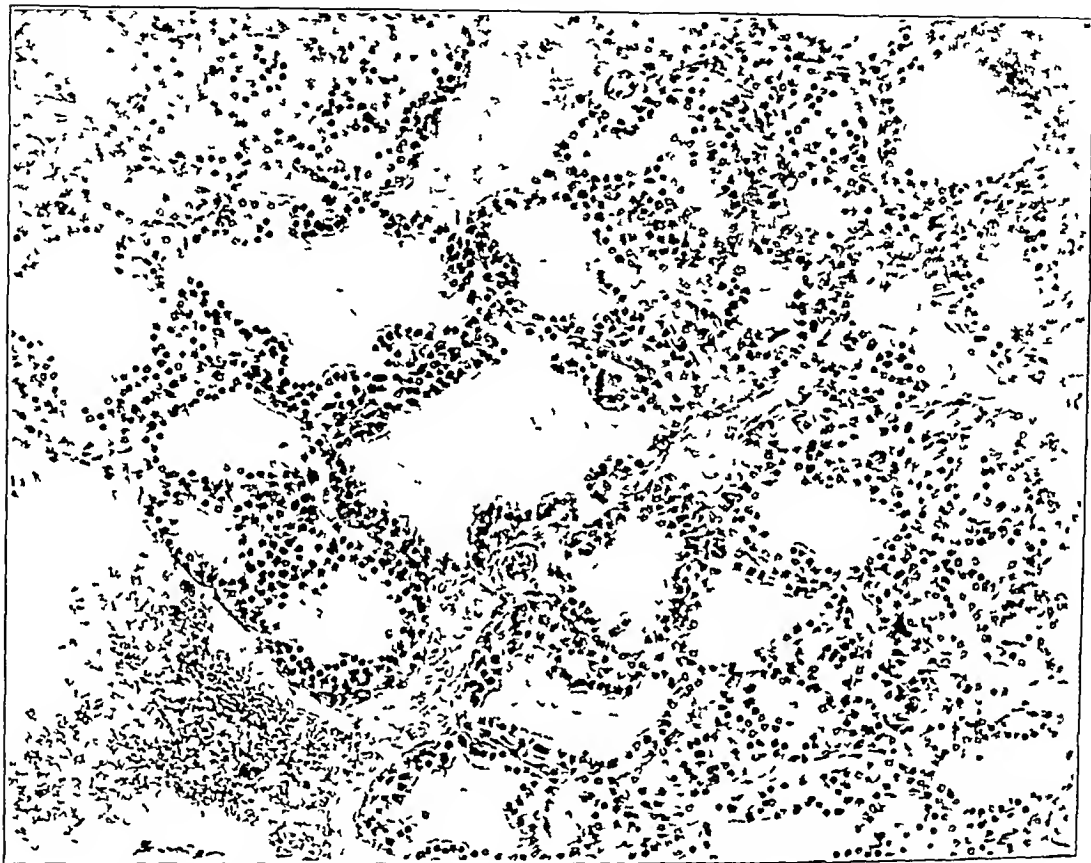


Fig 5—Section from the same thyroid gland as shown in figure 4, but removed from the dog following death caused by ingestion of 0.35 Gm of theophylline per kilogram of body weight forty hours previously. Hyperplasia is the most prominent feature seen, although desquamation with decrease in size of the acini is present.

8 Even when confronted by the fact that the methylpurines will produce hyperplasia of the thyroid cells in dogs, we wish to emphasize that one cannot assume by analogy that the ingestion of methylated purine bases in beverages as consumed by human beings would have any influence on the production of hyperplasia in the thyroid gland. In the first place, if a relationship between methylpurines and hyperplasia of the thyroid gland exists in the human body, the offending chemicals would most likely be present as by-products of the destruction of protein. Moreover, the amount of methylpurines ingested in beverages would not be sufficient to exert any effect on the thyroid gland on the scale of dosage and effect in animals would apply to human beings.

(Kruger and Salomon⁹) probably have their derivation from ingested methylpurines, such as caffeine, etc., the fact still remains that the human body is able to methylate certain compounds and does so normally. In support of this statement such methylated compounds as creatine, creatinine, choline, epinephrine and neuine are found in the human body. Choline itself is present in the thyroid gland.

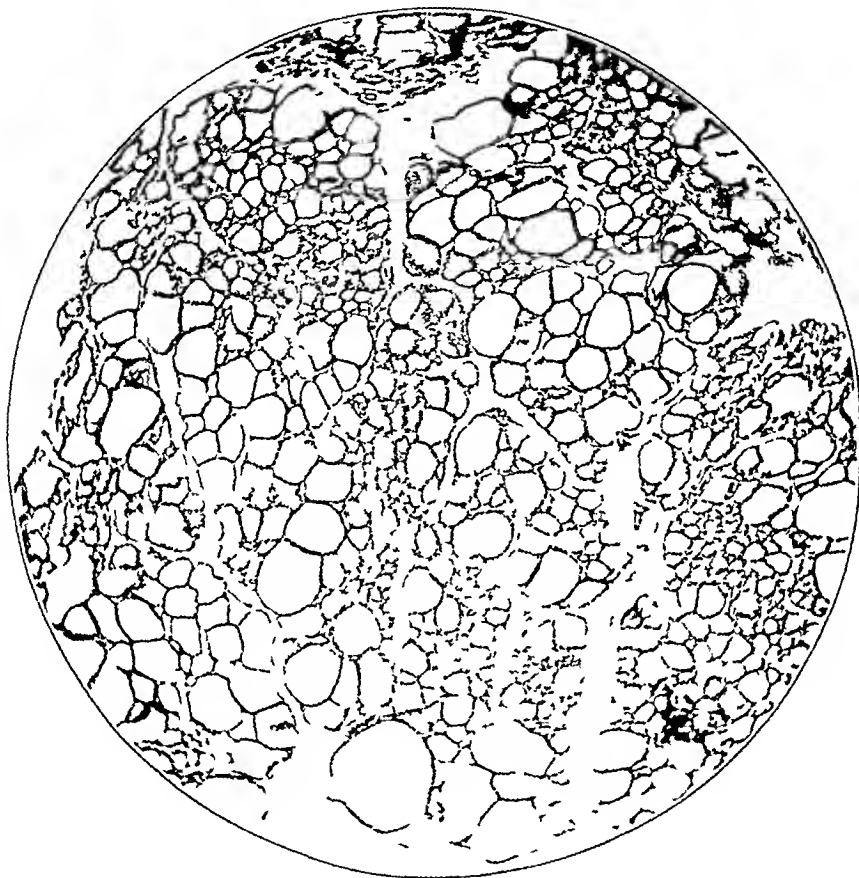


Fig. 6—The appearance of the thyroid gland of a dog several days previous to experimentation. See figure 7.

A large number of chemical compounds (ninety) were studied with regard to their effect on the dog's thyroid gland. Of this group, caffeine, theophylline and theobromine were found to exert the greatest effect, especially of the hyperplastic type, on the animal's thyroid gland. A larger group (eleven), including xanthine, guanine, pyridine, quinidine, histamine, etc., were found to produce changes of a milder character. (Our attention was directed to quinine by Dr. Leon Bromberg.) The rest of the drugs used produced no effect on the thyroid gland, even

⁹ Kruger, M., and Salomon, G. Die Alloxurbinen des Harns. *Ztschr. f. physiol. Chem.* 26: 350, 1898.

when given in lethal doses. It should be emphasized here that few drugs would produce marked changes unless given in toxic doses. We attempted to give all drugs in sublethal or lethal doses. It seems significant that practically none of a large series of inorganic drugs used produced any changes in the thyroid gland. For example, a dog weighing 10 Kg. was given 1 Gm. of copper sulphate orally per day for three days. The dog died on the day following the last dose. The liver

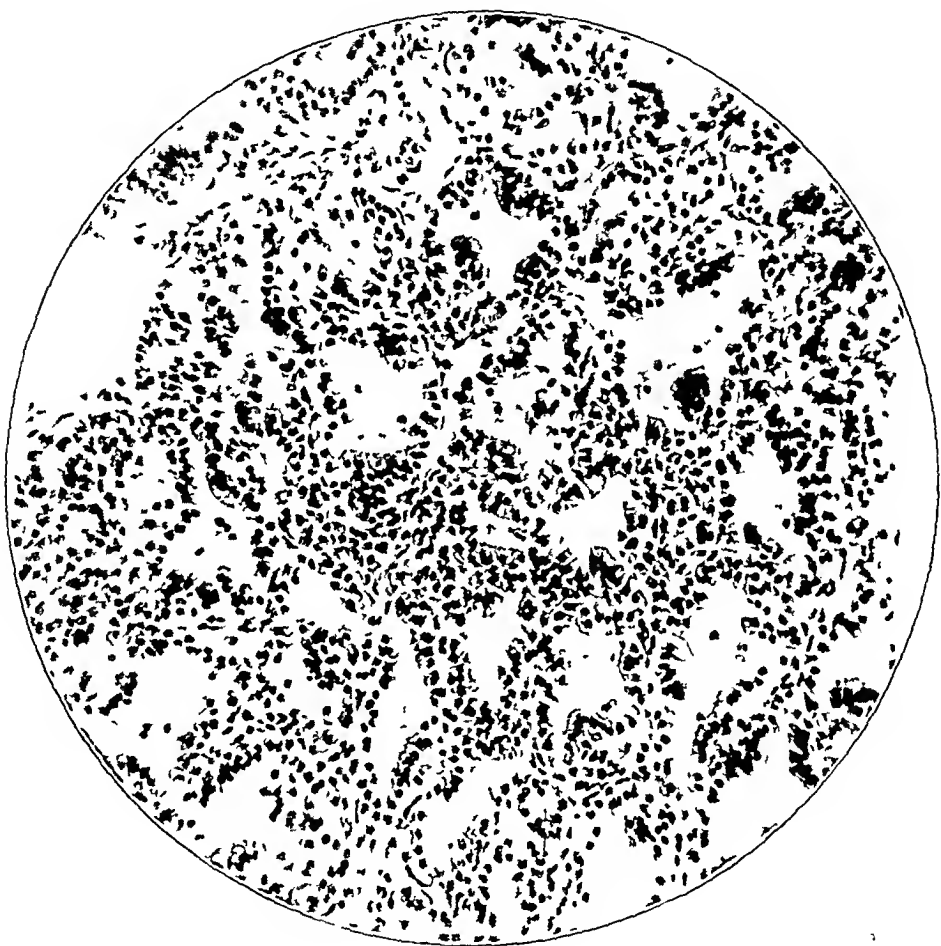


Fig. 7—Section of the same thyroid gland as shown in figure 6, after the administration of 0.3 Gm. of theophylline per kilogram of body weight on one day, followed by a dose of 0.6 Gm. of theophylline the following day. This section was taken after death, which occurred about thirty-five hours after the first dose. Note the extreme grade of hyperplasia produced by the drug. However, such a severe grade of hyperplasia is produced only occasionally.

and kidneys revealed massive destruction of cells with hemorrhages everywhere but the thyroid gland appeared normal.

On numerous occasions sections were removed from the thyroid gland of a dog under ether anesthesia and another biopsy was performed from one to four days later to determine whether or not the anesthesia

and the operation produced any changes in the thyroid gland. No change was observed except in one instance in which a loss of colloid with mild desquamation was noted in the thyroid gland of a dog in which a second biopsy followed the first by an interval of only one day. On the basis of this experiment, we now allow an interval of from three to four days to elapse after biopsy before experimentation. All animals with infected wounds following biopsy were discarded.

SUMMARY

In attempting to explain the effect (hyperplasia, desquamation, loss of colloid and iodine content) of certain infections and toxemias on the thyroid gland, which we and others have observed, we encountered certain noteworthy facts. The methylpuines—caffeine, theophylline and theobromine—on certain occasions produce a hyperplasia of the thyroid cells which is almost indistinguishable from the hyperplasia seen in the toxic goiters of human beings. We feel that since these drugs are so similar to the products of protein catabolism (especially those of nucleoproteins) the effect may be dependent on toxic by-products formed during the destruction of protein. It must be admitted and emphasized that the results obtained from the administration of most of the other drugs used in this series are subject to correction since many of the drugs were used on only one or two occasions. We do feel, however, that the production of a marked degree of hyperplasia following the administration of certain drugs is significant, even though it does not occur in every instance. As a whole, inorganic drugs apparently do not produce many changes in the thyroid gland in animals, even after the administration of fatal doses. The results obtained in this report are preliminary. Further investigation is being done on the effects of drugs especially of the by-products of destruction of protein, on the thyroid gland in animals.

THE FUNCTIONAL DISTURBANCES CAUSED BY THE INCONSTANT BONES AND SESAMOIDS OF THE FOOT*

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AND
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NEW YORK

Much material has accumulated on the anatomic and roentgenologic aspects of the inconstant bones and sesamoids of the foot. The works of Pfitzner, Gruber, Bardeleben, and Dwight are classic. Much less, however, has been said on the ability of these bones to cause functional derangements of the foot.

We have been impressed, both from a study of the literature and from our experience in the foot clinic of the Hospital for Joint Diseases, with the frequency of these bones, and with the uncommonness of functional disturbances associated with these little bones. Many of these ossicles, from their unprotected position, are exposed to trauma. Most may be liable to any disease process that may affect any other bone, also, they may disturb the statics and dynamics of the foot. In our series—an analysis of 1,000 roentgenograms of the foot, with a study of 336 available histories of the 596 patients in the series—we have stressed the ability of these bones to produce functional disturbances of the foot. We have avoided any detailed anatomic, anthropologic and physiologic discussion, except so far as they affect our understanding of the situation.

The inconstant bones and sesamoids considered are os trigonum, accessory scaphoid or os tibiale externum, os peroneum, styloid epiphysis and os vesalianum, os intermetatarsale, calcaneus secundarius (and calcaneonavicular fusion), os supranaviculare, secondary astragalus, os paracuneiforme, os subtibiale, bipartite internal cuneiform, bipartite cuboid, os proprium sustentaculi, cuboides secundarius, os inconstant sesamoids of the great toe, and inconstant sesamoids of the other toes.

These ossicles are often called accessory bones. We think that the term inconstant bones is more appropriate since almost every one of

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these bones has a separate cartilaginous center, preformed in the human embryo as early as the second or third month of fetal life, as proved by Bardeleben and others. Many of these ossicles are constant skeletal parts of the feet of lower mammalia. The majority of authors agree that these bones are to be considered as rudimentary elements inherited from the lower animals and present only in a more or less limited number of human feet.

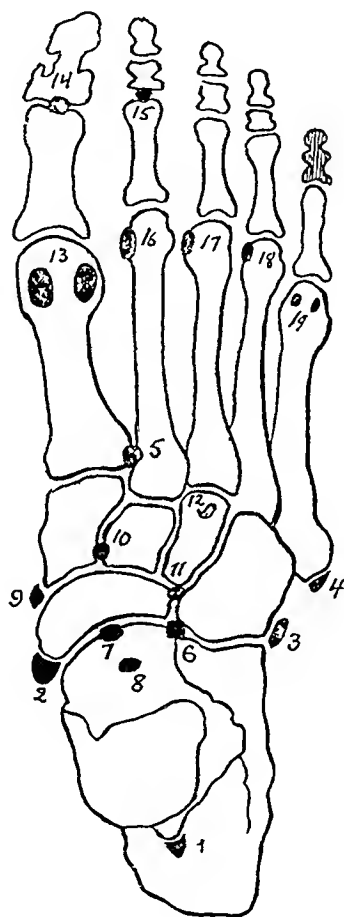


Fig 1—Diagrammatic ground plan of the inconstant bones and sesamoids of the foot. 1, os trigonum, 2, accessory scaphoid, 3, os peroneum, 4, styloid epiphysis and location of the disputed os vesalianum, 5, os intermetatarseum, 6, calcaneus secundarius, 7, os supranaviculare (seen laterally best), 8, secondary astragalus (seen best on lateral view), 9, os paracuneiforme, 10, os intercuneiforme (not described in text, since it can not be seen by roentgen examination and has no practical importance), 11, cuboides secundarius, 12, os unci, 13, constant sesamoids of the great toe, 14, interphalangeal sesamoid of the great toe, 15, interphalangeal sesamoid of the second toe, 16, 17, 18 and 19, inconstant sesamoids of the other toes. The shading of the terminal phalanges of the fifth toe represents the not uncommon fusion of the middle and terminal phalanx into one solid piece.

THE OS TRIGONUM

The normal posterior external tubercle of the astragalus is small. In our study, and in accordance with the concept of many authors (Gray, Dwight, Holland, and others), we have considered any enlargement or elongation of the posterior external tubercle due to fusion of the os trigonum with the small posterior external tubercle. Gray wrote "This process (posterior external tubercle) is sometimes separated from the rest of the talus and is then known as the os trigonum." It is not

TABLE 1—*General Statistics With Relative Frequency of Occurrence of the Different Inconstant Bones*

	Total Number
Patients	596
Histories examined	376
Roentgenograms of feet	1 000
Roentgenograms of feet showing an accessory bone or sesamoid anomaly	716
Negative feet	284
All age groups represented	
	Roentgenograms
Os trigonum noted in	493
Accessory scaphoid noted in	206
Os peroneum noted in	143
Styloid epiphysis of the fifth metatarsal noted in	43 of
(There were 92 patients between 9 and 15 years of age, representing a total incidence of this epiphysis of 26.1 per cent)	24 patients
Calcaneus secundarius noted once	
Os supranaviculare noted in 2 roentgenograms	
Secondary astragalus noted in 2 roentgenograms	
Os paracuneiforme noted in 1 case, bilaterally present	
Os intermetatarsaleum noted 33 times	
A combination of the os trigonum and the accessory scaphoid was noted 103 times of the os trigonum and the os peroneum 35 times	
A combination of the accessory scaphoid and the os peroneum was noted 23 times. A combination of the os trigonum, accessory scaphoid, and os peroneum was noted in 40 cases	

unusual for this fused os trigonum to form a large, thick blunt process projecting posteriorly and possibly even abutting against the posterior rim of the tibia. Gallois and Japiot noted the posterior apophysis as from 10 to 14 mm long in about 50 per cent of their cases, Mouchet and Bey noted a large posterior process in 38 per cent, Pfitzner in 14.3 per cent.

The secluded position of the os trigonum shelters it from trauma. It is for this reason that the bone has so little functional significance. Fracture of the free os trigonum is rare and seems to be almost impossible. The smaller the bone the more difficult will it be to fracture it. Scherliess noted that in flatfoot the inwardly displaced astragalar head may render a fused or free os trigonum, projecting outwardly, more exposed to injury. A study of the literature reveals an old furor over the so-called Shepherd's fracture. Shepherd himself, later realized that

his posterior fracture of the astragalus was only the free os trigonum. Experimentally, he was unable to duplicate this fracture. Cloquet and Hyrtl had made the same mistake many years before Shepherd. The work of Bardeleben and others established the os trigonum definitely as an inconstant bone. More recently, several observers, notably Patel and Bertrand, and Mouchet and Bey, have again brought up the possibility of Shepherd's fracture. After reading their articles, it is evident that they are impressed with the difficulty of diagnosing fracture from the os trigonum.

Menard has emphasized the fact that the appearance of the os trigonum, fused or free, is symmetrical. This is not necessarily true and the general consensus denies Menard's views. It is not so uncommon to find the os trigonum free on one side and fused on the other. Bilateral fusion of the os trigonum is by far the most common observation. The consideration of symmetrical bilaterality, then, is not an

TABLE 2—*Analysis of the Os Trigonum*

Os trigonum, fused or free, noted	493 times
Os trigonum noted free in	64 cases
Os trigonum bilaterally free in	14 cases
Os trigonum unilaterally free, other side not known, in	27 feet
Os trigonum free one side and fused on the other side in	9 cases
Os trigonum bilaterally fused in	102 cases
Os trigonum unilaterally fused, other side not known, in	115 feet
In a few cases, arthritic changes were seen in the os trigonum, other wise, no changes of functional importance were observed	

important point in the determination of fracture of the os trigonum. However, it is always best to have roentgenograms made of both feet for comparison. It should also be remembered that the os trigonum may rarely be bipartite or show a partial splitting. We have seen one such case. Pirazzoli, in a recent article, wrongly considered a partial splitting of the os trigonum as fracture. Some attention also has been given to the line of articulation between the os trigonum and the astragalus. It is usually smooth and clear, but occasional irregularities are observed, much as in the line of articulation between the accessory scaphoid and the scaphoid. Serration of the articular edge or fragment edges, with displacement of the fragment or fragments, may take place in fracture of the os trigonum. Pain about the posterior aspect of the ankle, on either inner or the outer side, may be due to many different lesions, and the coincidental presence of the free os trigonum need not be considered fact enough for the diagnosis of fracture. Bizarrio noted a fracture of the os trigonum due to a rifle bullet.

On the other hand it is much more possible to find fracture of a large posterior process the detached fragment simulating a free os trigonum. A forced plantar flexion of the foot with the large posterior

process impinging against the posterior border of the tibia may fracture both the process and the posterior rim of the tibia. Forced dorsiflexion of the foot, with torsion of the posterior talofibular ligament (which inserts partially on the free or fused os trigonum) may detach a fragment. There may often be an associated fracture of the

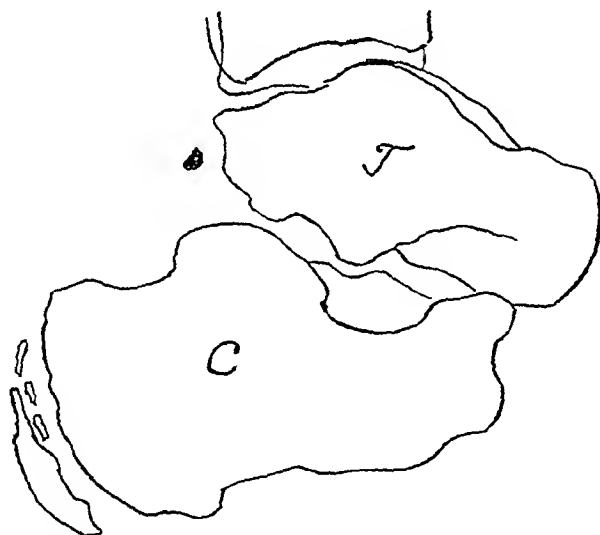


Fig 2—Beginning nucleus of ossification in the os trigonum, in the foot of a child, about 8 years old. In this and the following illustrations the abbreviations are as follows: *Ca*, os calcis; *T*, os talus; *A*, os astragalus; *S*, os scaphoid; *F*, fibula; *Cu*, os cuboid; *C I*, os cuneiform I; *C II*, os cuneiform II; *C III*, os cuneiform III; *Ti*, tibia.

os calcis or of the astragalus with jamming of the process onto the os calcis. We recently saw a roentgenogram in which was shown a crush fracture of the os calcis with jamming downward of the large

posterior process of the astragalus onto the os calcis. The process, however, was not fractured. Bastrup recently described several cases in which the posterior processes were enormous, long and large enough even to block normal plantar flexion. Eiken mentioned seventeen undoubted and six doubted fractures of the posterior process, in conjunction with fracture of the os calcis. In only one case was there an isolated fracture of the process. Lilienfeld noted that infraction of the posterior process is not so uncommon, both in his experience and in the literature. Dwight mentioned the fact that a loosely attached os trigonum might be pulled off by sprain of the attached ligament. It is doubtful whether the cases of Scheiliess, Van Assen, Ebbinhaus and Vollbrecht are true fractures, the assumed fragment looking much like the os trigonum.

Clinically, it is noticed that the foot is held in the equinus and sometimes in the valgus position. There is definite tenderness about the ankle, usually posteriorly and medially. Flexion of the great toe may be painful, in view of the fact that the flexor hallucis longus lies in a groove, the outer border of which is formed by the posterior external tubercle. Weight-bearing is painful, and there may be an associated limp. Pain may be increased on dorsiflexion of the foot, and crepitation may be heard. There may be present associated fracture of the os calcis, the astragalus or the tibia. There is, of course, a definite history of trauma. The roentgenogram shows the detached fragment, no longer in the direct axis of the astragalus. The fragment edges may be serrated. Laquerriere stressed the fact that there must be an agreement between the clinical and roentgenologic signs. Treatment may be conservative or operative. A roentgenogram taken several weeks after the original accident should show the presence of callus, according to Nion.

Isolated disease of the os trigonum is rare. Ratto and Casanovas described a case in which, following a dog bite about the posterior aspect of the ankle, two fistulas developed, which discharged a sero-sanguineous pus. A probe passed through the external fistulous opening struck bone—the os trigonum—and the persistent presence of the fistulas was attributed to disease of this bone. The os trigonum was removed with subsequent cure of the patient. The duration of symptoms had been two months. It is unfortunate that no microscopic study of the removed bone was made. It is our opinion that this was not an osteomyelitis of the os trigonum but an inflammation of the soft tissues posterior to the ankle. The preoperative roentgenograms showed the bilateral presence of the os trigonum. Mouchet and Moutier noted an osteitis of the os trigonum in a boy aged 13½. No details of the case are given. We have never seen epiphysitis of the os trigonum. The os trigonum develops from a separate center of ossification pre-

formed in cartilage at the second month of fetal life, which tends to ossify at about the eighth or ninth year. We have seen several roentgenograms of children's feet with small nubbins of ossification, representing the os trigonum. Arthritic changes in the os trigonum may be seen at times, usually in connection with a subastragaloid arthritis. Krida removed such a bone recently that was markedly enlarged by irregular osteophytes. Pfitzner found one os trigonum which was divided into several irregular pieces, a condition he thought pathologic.

Tumor of the os trigonum has never been reported.

THE ACCESSORY SCAPHOID

It is only the very large accessory scaphoid that usually gives rise to functional disturbance of the foot. The small accessory scaphoid or the accessory scaphoid with multiple centers of ossification is lost in the soft tissues posteromedially to the scaphoid and seldom causes trouble. The local effects of the large accessory scaphoid are due to the projection of this bone, medially or posteromedially. Feie and Denker, impressed by the marked prominence of this bone, called the condition exostosis. The shoe may press against this bony prominence, causing an area of redness, tenderness to pressure and sometimes swelling, the more so if the foot is turned in valgus. The skin may become thickened over the bone, and a protective bursa, which may be the site of an inflammatory reaction, may develop. No case of suppuration of this bursa has been described. Irritation of the tendon sheath of the tibialis posterior tendon is possible, according to Geist. Pfitzner has well described the variations of the tendon sheath, the tendon of the tibialis posterior, the bursa and the ligamentum calcaneonavicularis which may exist in the presence of accessory scaphoids of varying size. Thus tenderness may be present over the medial part of the tendon and over the medial fibers of the ligamentum calcaneonavicularis both of which send fibers to the accessory scaphoid. Gaugele noted that a periostitis of the accessory scaphoid may develop from the constant small traumatizing of the bone. This tenderness must be distinguished from the not uncommon tenderness over the scaphoid in weak foot. One should also note the amount of motion of the accessory scaphoid over the scaphoid. Many authors (Bressot, Capette, Elmslie, Rendu and Pouzet-Santy, and others) have reported cases of such tarsalgia due to the presence of the accessory scaphoid. Cure is easily effected by conservative means though many surgeons have removed the accessory bone.

Fracture of the tuberosity of the scaphoid is rare and the detached fragment resembles the accessory scaphoid. The appearance of fracture

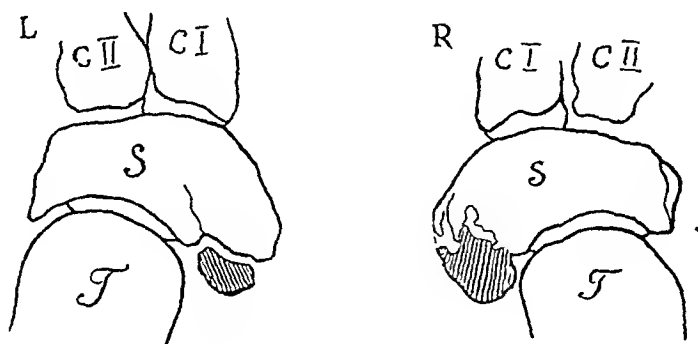
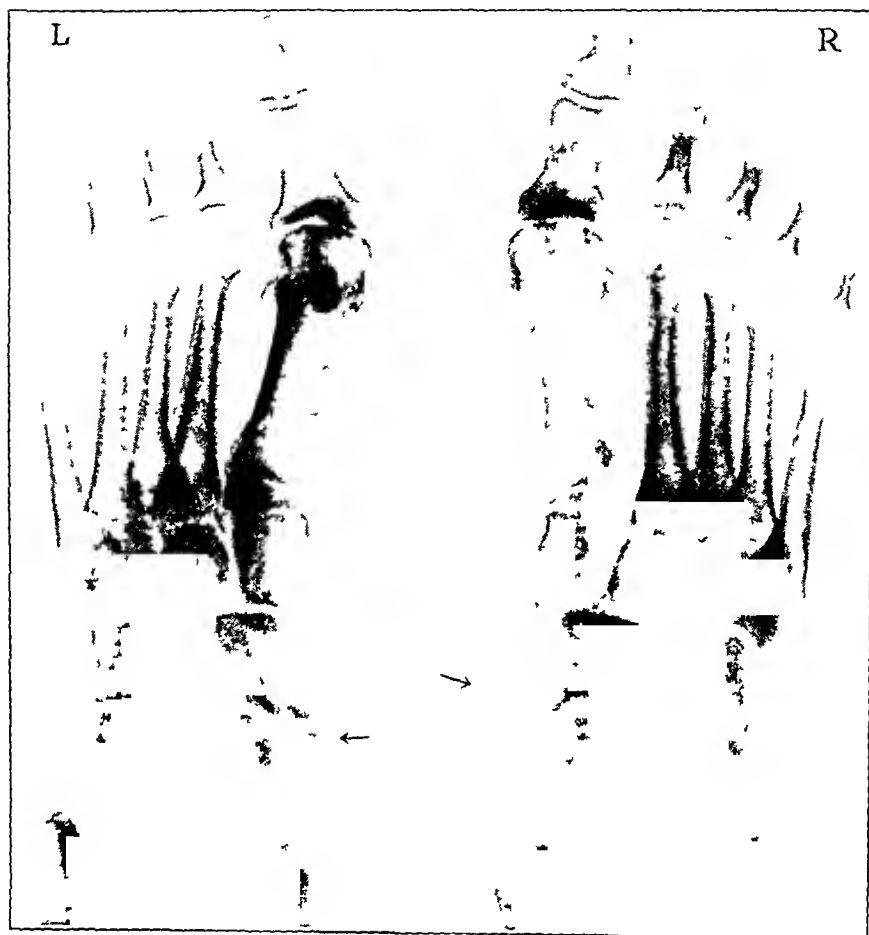


Fig 3—The accessory scaphoids are bilaterally present in the feet of a young woman about 30. Tenderness and pain were marked over the right accessory scaphoid following a sprain. The symptoms plus the roentgenographic appearance of the inconstant bone strongly suggested a fracture of the tuberosity of the scaphoid. However a view of the foot taken in an oblique plane was more suggestive of accessory scaphoids. This case illustrates the difficulties that one may sometimes meet with in differential diagnosis with fracture.

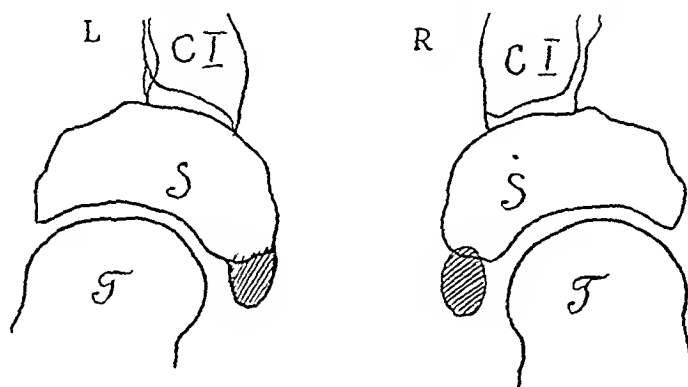


Fig 4—On the left side suggestion of beginning fusion of the accessory scaphoid to the scaphoid is seen. In this patient a girl aged 13 definite tenderness and pain were present over the left accessory scaphoid.

may be so striking that one may be tempted to diagnose the true accessory scaphoid as fracture, especially if there is a history of trauma. Many observers (Bazert, Horowitz, Haglund, Painter and others) have made such an error. The Haglund-Lilienfeld controversy created a situation as interesting as the fight over the legitimacy of Shepherd's fracture. Haglund then maintained definitely that his cases were cases of fracture and not of accessory scaphoid. Case reports on actual fracture of the scaphoidal tuberosity are rare. Nicoletti, Lilienfeld, Mouchet and Landwehr having seen cases. In Landwehr's case there was an associated fracture of the body of the scaphoid. Abadie and Rauge noted in their study of fractures of the scaphoid that the tuberosity may be detached. A differential point, aside from the serration of the fragment edge or associated fracture of other bones, is inversion of the base. The accessory scaphoid when triangular has its base externally and its apex internally, in fracture of the tuberosity the base of the fragment is said to be internal. We have not seen this, however. It should be remembered that this fracture is uncommon, whereas the accessory scaphoid is frequently seen. The burden of proof is on the observer. Fracture of the tuberosity in the presence of a large accessory scaphoid has never been reported. Fairbank mentioned the case of a woman, aged 51, with a definite tarsalgia of about a year's duration. The accessory scaphoid was bilaterally present, but he thought the right one was fractured. Bipartite tarsal scaphoid (Froelich-Pirie), fracture of the body of the scaphoid and Kohler's disease of the tarsal scaphoid are easily differentiated.

Isolated disease of the accessory scaphoid has been reported. Arthritis of the line of articulation between the accessory scaphoid and the scaphoid is not unusual and is manifested roentgenographically by a haziness and irregularity of the joint surface. Clinically there is definite tenderness over this joint with possible evidence of other arthritis in the foot. Dwight noted that there was a tendency of the cartilage of the joint to degenerate with resulting interlocking of the apposing joint surfaces. Pain may be felt in the natural fusion of the accessory scaphoid to the scaphoid. This was noted by us in one case in a young adult. We have seen in a Negro, 55 years of age detached irregularly round osteophytic particles from the scaphoidal tuberosity which resembled the accessory scaphoid. The foot was strongly arthritic and there was some resemblance to Charcot's disease.

In a previous note we described the case of a girl aged 8½ who had an unusual change in the accessory scaphoid and in the styloid epiphysis of the fifth metatarsal which was interpreted as epiphysitis. There was that fluffiness that irregular patchiness of the bone which suggested it strongly. There was complete restitution nine months later. Fairbank several years before mentioned that he had seen two such

cases One of us (L.) has learned of two other cases at the Hospital for Ruptured and Crippled (service of Dr Percy W Roberts) In one case, the bone was removed, but unfortunately the specimen was lost This condition should not be confused with a postulated and most probably theoretical epiphysitis of the posterior apophysis of the scaphoid, especially when it has a separate center of ossification according to Froelich Fairbank, in 1924, also described a condition of the accessory scaphoid similar to Kohler's disease of the tarsal scaphoid There was noted fragmentation of the bone into two or more pieces, with condensation of the fragments He terms this osteochondritis of the accessory scaphoid Froelich, in 1913, also noted a similar condition Japiot believed that an inflammation of the accessory scaphoid might give rise to a tarsalgia of adolescence The pathologic process in the aforementioned diseases can only be inferred, since no specimens have been available for examination Clinically, the conditions may be symptomless or there may be pain and tenderness over the accessory bone Froelich believed that there might be an osteitis of the accessory scaphoid due to infection with staphylococci of low virulence, as seen in one of his cases Undoubtedly, the staphylococci in his specimen were due to secondary contamination Froelich also believed that the presence of the accessory scaphoid rendered the midtarsal joints more open to infection This has not been substantiated Poncet's theory of fibrous tuberculous, and Kirrmisson's theory of rheumatic, infection of the accessory scaphoid have not been upheld Several authors (Bedart Étienne) have mistaken redness and tenderness over an accessory scaphoid in tuberculous children as a tuberculous osteitis of the scaphoid, till a roentgenogram disclosed the presence of the accessory bone, to which all symptoms were due Monahan's theory that the accessory scaphoid is present only in cases of constitutional disease is unwarranted

Tumor of the accessory scaphoid has not been reported

From the orthopedic standpoint, the major interest in the presence of the large accessory scaphoid is in its relation to flat feet One may state that the accessory scaphoid may be present in a foot which is flat or not The appearance of flatfoot may be suggested by the downward and inward projection of the inconstant bone An analysis of such a foot will show that the forefoot and backfoot are in normal relation to each other Gaugele noted that the presence of a weak foot is only incidental and that the valgus position of the foot only exposes the inconstant bone to more trauma In most of Geist's cases, a weak foot was not present, Hohmann noted the opposite Zadek has pointed out that the major insertion of the tendon of the tibialis posticus is altered in the presence of the large accessory scaphoid the insertion being mainly on the undersurface of the scaphoid Together with this it was

noted by Kidner that there is an inward, and possibly an upward, displacement of the tendon of the tibialis posticus. He then said that the alteration of the line of pull of the tendon and the alteration of its insertion tend to diminish the effect of the tibialis posticus as a supinator of the foot. The muscle in contracting must contract more strongly, since it is pulling at an angle, tending to weaken it and thereby diminishing its lifting power on the center of the arch of the foot. We do not believe that the slight inward deviation of the tendon of the tibialis posticus by even the largest of accessory scaphoids (from 1 to 2 cm. at the most) will result in a foot working at such a mechanical disadvantage that flatfoot will result. We believe that flatfoot is independent of the accessory scaphoid as a primary factor in its production and that when the two exist together the relationship is incidental and not causal. Our experience substantiates this. It has also been noted that there is some limitation of hyperadduction of the foot with pain at the extreme of motion. This again may be due to secondary arthritic changes or static changes, the presence of the accessory scaphoid being incidental. In the hyperadducted position of the foot, there may be a crowding together of the soft tissues, between the large accessory scaphoid and the internal malleolus. Actual contact has not been observed. This, then, may be a factor in the production of pain.

Sitenko seeks deeper and invokes that constitutional condition causing the disturbance in ossification, which delays the ossification of the navicular bone, in the presence of the accessory scaphoid. The navicular bone then, because of its delayed ossification, wedges itself in between the other, faster growing tarsal bones, thereby tending to flatten the arch. This statement is wrong, since the foot would go into adduction, as seen in congenital clubfoot, in which navicular ossification is delayed. Also while it is true that in the scaphoid the nucleus of ossification appears later than in the other tarsal bones, it must be proved that the presence of the accessory scaphoid will further tend to delay navicular ossification. In the light of the definite anthropologic history of the accessory scaphoid, there is no reason why it should delay navicular ossification.

We believe that as a rule the accessory scaphoid should not be removed. There is no longer a tendency to remove the accessory scaphoid on sight. Undoubtedly, the small and medium-sized accessory scaphoids should be let alone, the larger ones especially the long hooked ones, may be removed only if there is enough functional disturbance to warrant it. In all of our cases conservative treatment, physical therapy, proper support for the shoe and exercises have given good results. All the operations used remove the accessory scaphoid and part of the tuberosity of the scaphoid. Several supplementary measures may

be employed—shortening of the tendon of the tibialis posticus, astragalo-scaphoid arthrodesis and mobilization of the tendon after the method of Kidner

Of the 336 histories examined by us, only 17 mentioned symptoms referable to the presence of the accessory scaphoid (206 accessory scaphoids represented). In no case was the accessory scaphoid removed, although in a young girl, a bilateral Miller operation was done by Dr. H. Finkelstein. In 4 there was definite pronation of the foot, in all, tenderness and pain over the accessory scaphoid were present, in 3, there was definite limitation of hyperadduction of the foot while in only 1 were there bilateral symptoms. In 1 case, there was a gouged out area in the scaphoid bone, with tenderness and swelling, in the presence of the accessory scaphoid. It is questionable whether symptoms should be attributed to the accessory scaphoid. The Wassermann reaction was negative. Age groups represented here are first decade 1, second decade, 7, third decade, 3, fourth decade, 4. One patient was 43 and another 53. No attention was paid to sex in its relation to symptomatology in the presence of the accessory scaphoid.

THE OS PERONEUM

The os peroneum, wrongly called a sesamoid in the tendon of the peroneus longus, has seldom been considered as a factor in the production of tarsalgia. Stiopem, in 1920, reported a case of multipartite os peroneum, which he considered as a fracture. Histologic examination of the excised bone confirmed the diagnosis. His patient was an obese woman who fractured the bone in a momentary strong supination of the foot.

The bipartite character of the os peroneum has been noted often, more recently than in the purely anatomic era of Pfitzner and Gruber. No figures have been available as to how often the os peroneum is divided. We have noticed division of the bone in 34 cases (bone noticed 143 times in all), double division, 27 times, triple division 6 times and multipartite (4 or more pieces) once. There is, then, a definite tendency for the os peroneum to split. Lihenfeld and Pfitzner comment on this as an expression of greater regression of this inconstant bone.

We have introduced these preliminary remarks as fundamental for the understanding of a syndrome type seen by us in four cases. These patients complain of pain on the outer border of the foot a variable distance behind the styloid process of the fifth metatarsal bone usually definitely localized in the region of the os peroneum. The pain is often sharp; it may be definitely localized or may radiate up along the peroneal muscles. The patient may be confined to bed in the acute stage. Manipulation of the foot into varus increases the pain. There is no remembered history of trauma although the patient may think that he

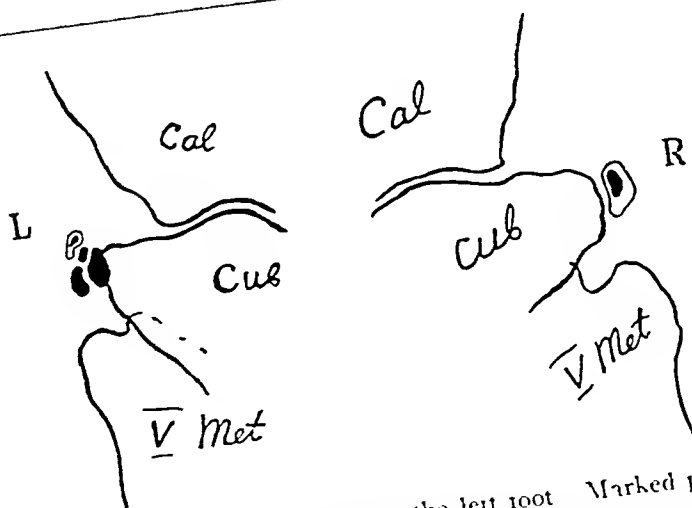
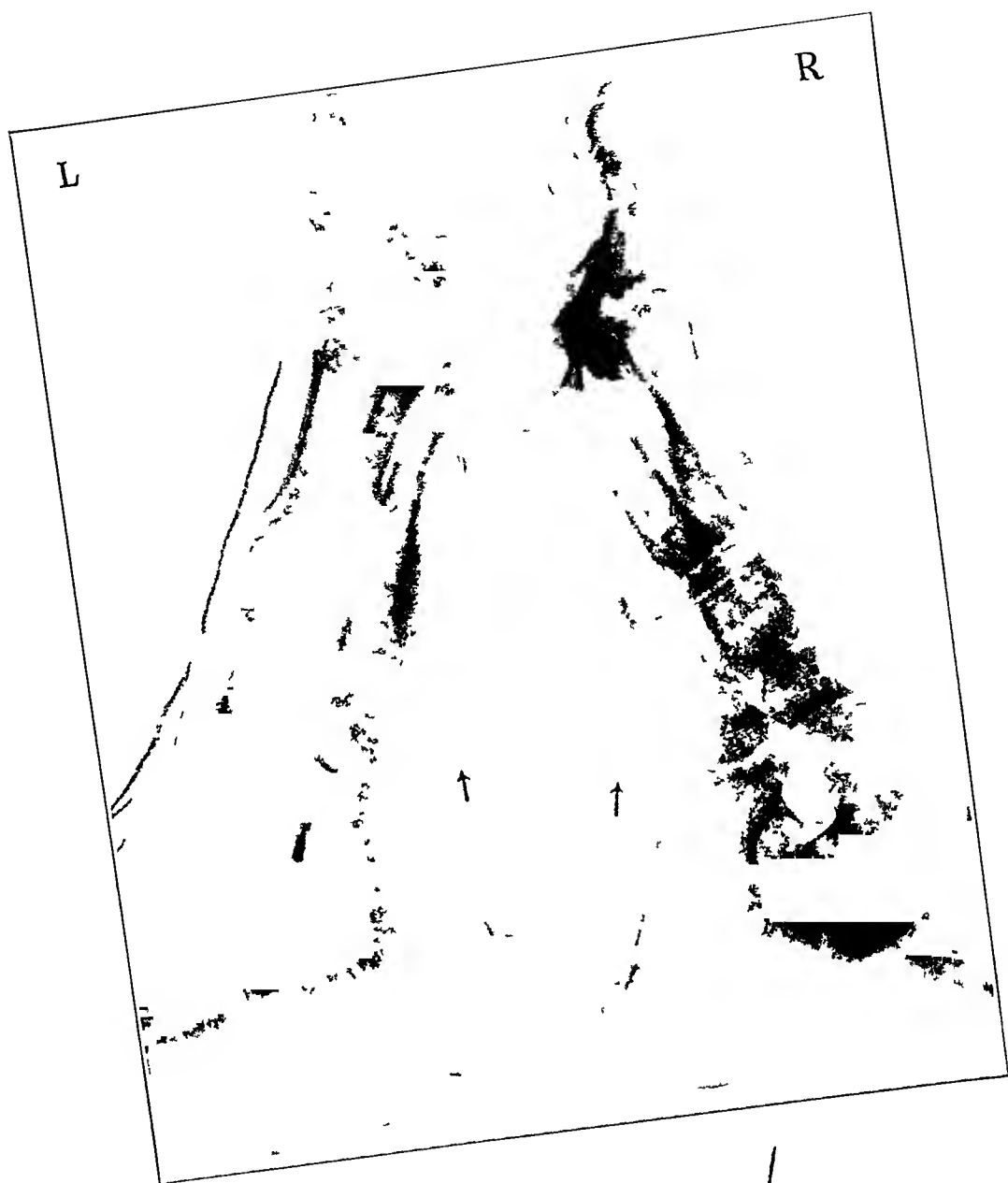


Fig 5—A multipartite os peroneum in the left foot. Marked pain and tenderness were present over the bone suggesting the possibility of fracture. On right side os peroneum is bipartite.

has slipped or twisted the foot in some way. There is no history of recent infection. In two patients, both women, a history of an acute onset was given. We saw one case in the acute stage. The patient had a definitely suggestive tenovaginitis of the peroneus longus. The other patient's history also suggested an old acute tenovaginitis of the peroneus longus. Following this acute onset, there is a duller pain on the outer side of the foot, localized in the region of the os peroneum, the pain varying in intensity and appearing and disappearing. A roentgenogram shows that, corresponding to the region of greatest tenderness, there is a multipartite os peroneum, the bone being divided into four, five, six or more unequal fragments. There is no regular line of division between these pieces. In one instance, we were able to diagnose the presence of the multipartite os peroneum from a consideration of the symptoms and signs before the roentgenogram was taken. It is most difficult to fracture a small slippery bone, partially enclosed in a tendon and protected by several layers of tissue thicknesses. Of course, the original presence of multiple centers of ossification may cause a predisposition to do so. The natural tendency of the os peroneum to regress must not be forgotten. Stropen's theory of the production of fracture is that the os peroneum is crushed by a sudden inadvertent supination of the foot, the bone being fixed by a contracted peroneus longus. It is unfortunate that we have not been able to obtain any specimen for examination. The patients, after receiving strappings and physical therapy, improved somewhat. Most of them did not attend the clinic long enough to warrant any estimation of end-results. It may be noticed that we have hesitated to call this syndrome type fracture of the os peroneum. We have not enough data to warrant this. In two other cases, with histories and signs suggesting this syndrome, no os peroneum was seen in the roentgenogram.

It is unlikely that the os peroneum may be confused with fracture of the cuboid or os calcis.

Isolated disease of the os peroneum has not been described. Japiot believed that an inflammation of the os peroneum might well give rise to a tarsalgia of adolescence. Arthritis of the occasional articulation between the os peroneum and the cuboid has not been observed. This articulation which is constant in the monkey, according to Gilette is always rudimentary in man, according to Pfitzner. Schuster saw a case in which an unusually large os peroneum in a foot lacking in adipose tissue caused much pain on the outer border of the foot when a tight shoe was worn. Tumor of the os peroneum as with the other inconstant bones has not been reported.

In transplanting the peroneus longus the os peroneum may be encountered.

THE STYLOID EPIPHYSIS OF THE FIFTH METATARSAL AND
THE OS VESALIANUM

Whether there is such a bone as the os vesalianum is still a moot question. It is apparent on examining the original drawings of Vesalius that he himself precipitated the controversy. The dorsal and plantar views of the adult foot he presents are apparently of different feet. The dorsal view is a drawing of an undoubted os peroneum, the plantar view represents a small bone just behind the styloid process of the fifth metatarsal. This may be a forwardly placed os peroneum.

At any rate, the styloid epiphysis of the fifth metatarsal is not the os vesalianum. It is a definite accessory epiphysis (Giuber, Iselin, Kirchner) present in children between the ages of 9 and 16. Schouwey, continuing the work of Iselin, noted this epiphysis as constant between the ages of 13 and 14, fusion taking place at about the age of 16. Delayed appearance may occur in those who are ill. Giuber noted this epiphysis 18 times in 124 fifth metatarsal bones which showed an epiphyseal line. Lambert Rogers noted this epiphysis in 28.7 per cent, in our series it was present in 26.1 per cent of cases. Fusion is definite, and we saw no case in a person over 15 or 16 years of age.

Diseases of this epiphysis are rare. In some children, we have noticed redness and tenderness over the styloid process of the fifth metatarsal, in which the styloid epiphysis on roentgen examination was normal. It is possible that this condition may be due to a tight shoe pressing on a prominent styloid process. Iselin has described a definite epiphysitis of this epiphysis. Our reported case showed a lesion of the styloid epiphyses bilaterally together with a similar lesion of the accessory scaphoids. There were no symptoms. Roentgenologically, the styloid epiphyses were enlarged and showed fluffiness, irregular areas of density alternating with lighter areas. There was a definite tendency toward restitution though this was not complete at the end of nine months.

The os vesalianum is a bony structure the existence of which it is necessary to prove with every case report. Any accessory bone must obey the postulates of Thilenius—that it is followed in the animal series that it is present in the fetus and that it is connected by hyaline cartilage with its supporting bone. Little anthropologic work has been done on the os vesalianum. It is supposedly the atavistic remains of a fifth distal tarsal bone such as that seen in the primitive reptile *Sphenodon*, in *Proganosaurus*, in *Didelphys* and in *Urodela*. It is also found in the tortoise. Spionck noted the os vesalianum formed in cartilage in a newborn child with polydactylia and other congenital deformities. This may possibly have been the distal tarsal element in the seventh ray, according to the ray theory of the development of the extremities (Debrere, Bardeleben, Albrecht, Bieri). One of Laquerriere's cases

showed a large, well formed, bony element on the outer side of the foot, distinctly resembling a tarsal element. Despite the fact that he calls it the *os vesalianum*, this too may be considered as a vestige of the seventh ray. The cases of Baastrup with the possible exception of one, show large bony elements, not in the least resembling the classic conception of the *vesalianum*. They are undoubtedly the large tuberosity of the fifth metatarsal bone partially detached, and probably may be a fracture of the tuberosity of the bone, since many of his cases have a history of trauma. Holland thinks that these are the separate tuberosity of the fifth metatarsal bone developing from a separate center of ossification and persisting throughout adult life. It is noted that the condition may be bilateral. He includes these bony elements in his second class of *vesalian* bone the first being the styloid epiphysis and the third the classic type of *os vesalianum*.

An analysis of each supposed case of *os vesalianum* reported is not within the scope of this paper. Suffice it to say that cases have been published by Gelinsky (one), Davis (one and probably the styloid epiphysis), Hasselwander, Froelich (two), Mouchet and Moutier (five), Metzger (one), Fischer (two), Johansson (one), Laquerriere and Dreyon (one), Holland (one), Mauclore (one) and Gruber (three questionable ones). Halle, Diemberioeck, Kulmus and Bartholinus mentioned the *os vesalianum* in the seventeenth and eighteenth centuries. Johansson noted that in his case the *os peroneum* was also present. To settle definitely the relation of this mooted bone to the styloid process and to the cuboid, roentgenograms in several planes—anteroposterior, lateral and several oblique—should be taken. Our impression from a study of the literature is that there is no bone that can be called *os vesalianum*. The so-called *os vesalianum* is either a forwardly placed *os peroneum* or a remainder of a seventh ray.

Any practical importance attaching to the *os vesalianum* if it exists, lies not so much in its rarity as in distinguishing it from fracture of the tuberosity of the fifth metatarsal bone. Such fracture is not unusual, and the tendency is to call this fracture the *os vesalianum* rather than the converse. A history of trauma, the signs and symptoms present and a roentgenogram of both feet should help materially in making the diagnosis. It is safer to err on the side of fracture. It should also be remembered that the existence of the *os vesalianum* is still disputed and altogether denied by us.

The appearance of the *os vesalianum* may also be duplicated by a forwardly placed *os peroneum*.

OS INTERMETATARSEUM

The *os intermetatarsium* is said to be the base of the atavistic first ray according to Lunghetti, Dwight, Pfizner and Volkov. Its location

between the bases of the first and second metatarsals may make it difficult to be seen. A dorsally placed os intermetatarsaleum may be seen on lateral view. It should not be mistaken for an arthritic exostosis or a calcification in a digital vessel.

Functionally, the os intermetatarsaleum is relatively unimportant. We have seen four cases in which it formed a dorsal and painful prominence, resembling an exostosis of the first cuneiform bone. In two of these cases, we were able to diagnose the presence of the bone before roentgenograms were taken. Young noted that the os intermetatarsaleum may be a factor in the production of a congenital hallux valgus. Schuster

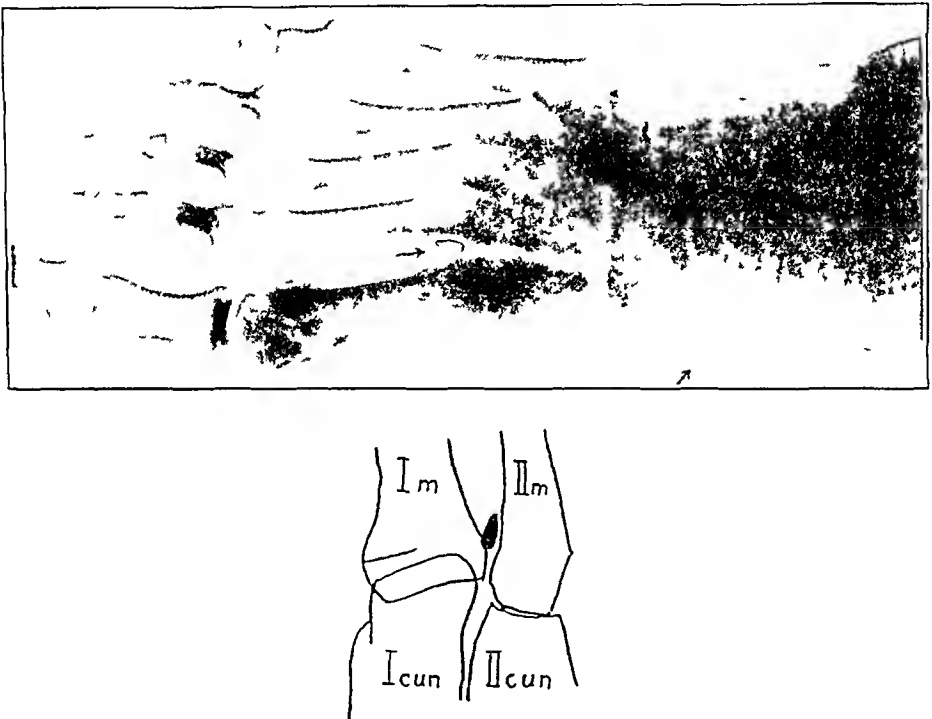


Fig. 6—Os intermetatarsaleum (retouched) and a large accessory scaphoid

said the same thing and believed that it may cause increased adduction of the first metatarsal with secondary abduction of the big toe. We have not noticed this.

This inconstant bone may possibly interfere in the operation of disarticulation of the tarsal-metatarsal joint.

CALCANEUS SECUNDARIUS AND CALCANEONAVICULAR FUSION

The calcaneus secundarius becomes important in disturbing the statics of the foot only when fused either by fibrous or bony union to both the navicular and the calcaneus—calcaneonavicular fusion. As a clinical and pathologic entity this was brought forth by Slomann in 1921. Pfitzner, Stieda, Holl, Sutton, Hamant, Prout, Dujarier

Morestin Zuckerkandl, Weber, Gruber and others had noticed the fusion in anatomic material. The manner of fusion, according to Pfitzner, occurred through the intermediation of the calcaneus secundarius, the quadrangular bone in the quadrangular space between the os calcis, scaphoid, cuboid and the astragalus. The calcaneus secundarius has been confused with two other bones, neither of which it is—the cuboides secundarius and a small bone, also called calcaneus secundarius by Dwight, at the front of the sustentaculum tali. We have not paid attention to the long anterior apophysis of the os calcis, which is con-

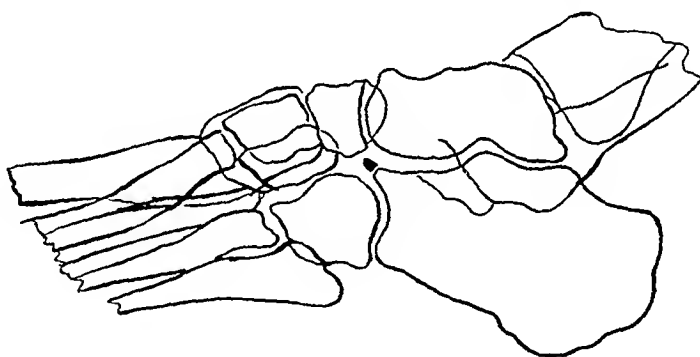


Fig. 7—Calcaneus secundarius

sidered by some to represent a fusion of the calcaneus secundarius to the os calcis. The two bones may be joined by amphiarthrosis, syndesmosis or synostosis.

Calcaneonavicular fusion is associated with important functional disturbances of the foot. Most cases show a definite and marked flat-foot noticeable even in the young but most noticeable at puberty. There is definite limitation of pronation and supination of the foot. The foot is often rigid and the peroneal muscles may be spastic. Ankle motion is normal. There may be muscle atrophy as pointed out by Chaput. The symptomatology varies with the degree and duration of the deformity. Symptoms are definitely increased during puberty. Not

many cases have been reported thus far. Slomann reported five cases, two in children and three in adults. He quoted Pannei as having seen three undoubted cases. Nove-Josserand, in 1923, cited two cases, both of which Slomann denied. Badgley, in 1927, reported five cases, Bargellini, in 1928, one case, and Bentzon in 1928 six cases. The fusion is uncommon, and misleading roentgenograms may tend to its diagnosis when it is not actually present. It is not unusual to see the anterior apophysis of the os calcis overlapping the scaphoid, simulating fusion, on the straight lateral view. An oblique view should show actual fusion best.

As with the accessory scaphoid, many theories have been set forth to explain the relation of calcaneonavicular fusion to the accompanying disability of the foot. We believe a simple mechanical explanation best. Lazarus believed the condition to be due to fetal persistence. In the new-born child he noted adduction of the foot with the cartilage of the os calcis in contact with the cartilage of the scaphoid. Separation occurred in the normal detwisting of the foot, the interosseous ligament forming in the newly formed space between the navicular and the os calcis. The synostosis is only a persistence of this early condition, with imperfect development of the ligament. Leboucq also noted this. Bargellini believes in no one special theory in view of the fact that there are multiple anomalies of the os calcis, scaphoid and astragalus. The multiple action of all these anomalies plus static factors will produce a tarsalgia, usually at the period of greatest skeletal growth. Slomann's conception previously enunciated in 1890 by Leboucq, we believe correct, namely, that the anterior component of body weight is transmitted through the body, neck and head of the astragalus, downward and forward to the navicular. Normally, this anterior component would pass through the navicular to the first cuneiform and first metatarsal bone. Owing to the fusion, there is a sudden stopping of the anterior weight forces at the navicular bone with direct transmission vertically to the foremost and innermost point on the os calcis. This tends definitely to pronate the os calcis, astragalus and scaphoid. Nove-Josserand stated that flatfoot is secondary to the tarsalgia which is due to a spasm of the extensor and peroneal muscles and to the diversion of articular movements to nearby joints because of the synostosis.

Because of the unusual pressure of forces at the talonavicular joint, osteo-arthritic changes may develop and complicate an already complicated disability. Treatment varies with the case from the conservatism of physical therapy, exercises, manipulations and plates to the more radical open operation—lengthening or excision of the peroneal tendons to relax spasm (Badgley), resection of the synostosis with or without interposition of the muscle belly of the extensor brevis digitorum to create pseudo-arthritis (Badgley, Bentzon), wedge resection of the

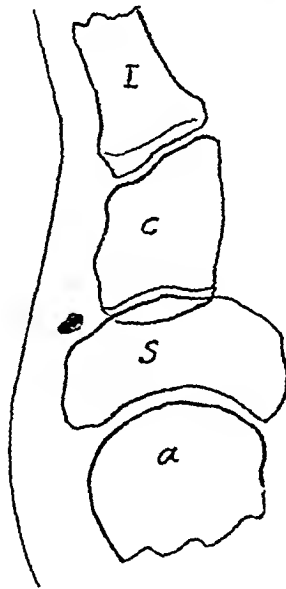


Fig 8—Os paracuneiforme (retouched) This is fairly well shown on the original plate although it has photographed indistinctly because of poor calcification of this bone, which evidently is undergoing degeneration

scaphoid to raise the longitudinal arch (Bargellini) and triple arthrodesis if the secondary arthritis is marked (Badgley). Krida removed a secondary os calcis with definite relief from pain for which the inconstant bone was blamed.

In our series we saw no case of calcaneonavicular fusion. We had only one case of unilateral calcaneus secundarius. (Although there was a history of a trauma, we believe this case to be a real inconstant

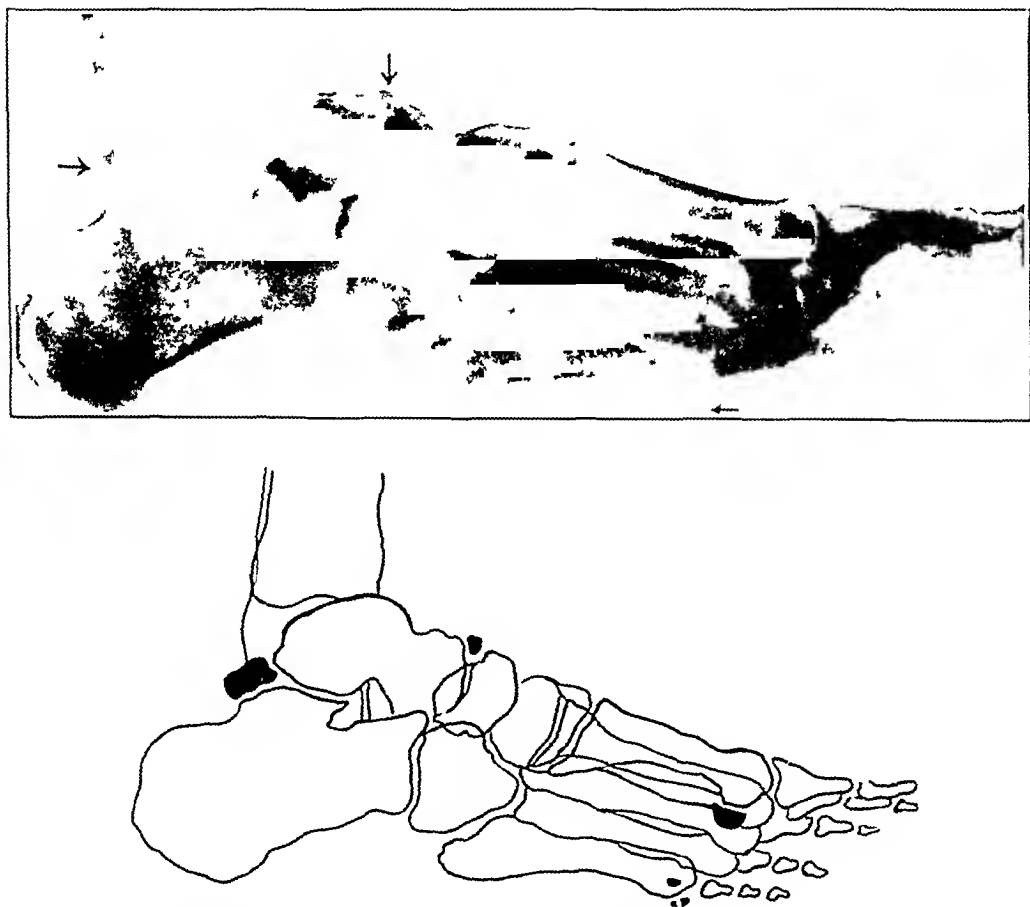


Fig. 9—Multiple anomalies in a foot: os supranaviculare, os trigonum and congenital division of the fibular sesamoid of the fifth toe.

bone but not a result of the injury.) Possibly some other cases might have been found if all the roentgenograms had been taken in the oblique plane.

The calcaneonavicular fusion like many other fusions may interfere in disarticulation of the foot at the midtarsal joint.

Calcaneonavicular fusion is the most common congenital fusion. Other types have occasionally been observed—calcaneo-astragalar fusion, calcaneocuboid fusion, astragalo-scaphoid fusion (astragalo-scaphoid bone), scaphoidenoid fusion. It is unnecessary to discuss these in this

paper, as reference may be made to articles by Leboucq, Anderson, Pfitzner, Ilievitz and others. These congenital fusions tend to disalign the statics of the foot and to alter its dynamics.

OS PARACUNEIFORME

This unusual bone, located between the scaphoid and the inner cuneiform bone, on the inner border of the foot, was first noted by

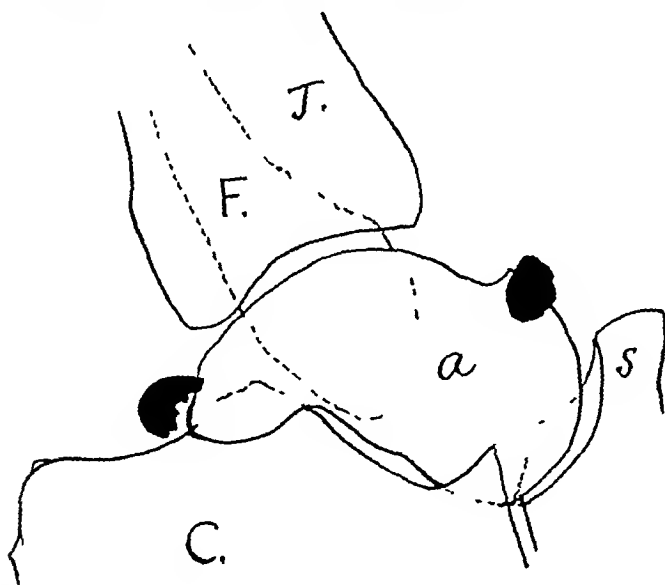


Fig 10—Secondary astragalus and a large free os trigonum

Dwight who thought it a pathologic formation. He compared it to the bone described by Pfitzner—the pars peronea metatarsalis primi—and said that possibly they were the same. Carlier and Cameron each described clinical cases in which the bone was noted as a projection on the inner border of the foot. In Carlier's patient a youth of 19 the bone had been present since birth but it had been growing rapidly in

the few months before examination. The skin was red and a small bursa was located between the skin and the bone. The bone was slightly movable laterally. A roentgenogram showed this inconstant bone against the inner side of the first cuneiform bone, a thin line of articulation separating them. The bone was removed. In Cameron's case, the bone had an articular facet for the scaphoid, an accessory scaphoid was also present on the same side. We have seen one case in which the bone was present bilaterally.

OS SUPRANAVICULARE

The os supranaviculare is located between the dorsal aspect of the astragalus and scaphoid, usually articulating with the latter, though it may also fuse with the astragalus. It may thus be fused or free. When fused, it may resemble an arthritic exostosis or a trochlear process. Paine, to whom discovery of this bone is credited, in 1919 described fourteen cases, one of which was bilateral. Pacini, in 1910, Campbell in 1918, and Wigoder, in 1928, noted this bone. This inconstant bone if it is one, is to be differentiated from fracture of the superior surface of the scaphoid. We have noted three instances of this bone, two in this series.

SECONDARY ASTRAGALUS

The secondary astragalus is round and located just behind and above the head of the astragalus. It may be fused or free and must be distinguished from fracture, arthritic exostosis, an inflammatory product, as of osteomyelitis, and a trochlear process which is not uncommon on the neck of the astragalus. It is possible that the trochlear process may be a fused secondary astragalus. No functional disturbance is attributed to this bone. In 1921, Bierman described this supernumerary ossicle in a patient with an old osteomyelitis of the tibia. We have seen two cases in this series.

OS SUBTIBIALE

The os subtibiale is an unusual pea-sized accessory bone located on the medial aspect of the foot just below the internal malleolus anterior to the astragalal facet. From a study of three cases Bircher believed it to be a sesamoid and said that it must be differentiated from pathologic calcifications in the ligamentum calcaneotibiale. Grashen, who saw one case, noted the same thing. Hawig and Pfitzner have also noted cases. Gray noted that sesamoid bones may be present externally or internally in the tendons turning about the ankle. Lupo said the position and morphology rule out its being a sesamoid bone. He expressed the belief that the line of separation is an articular line.

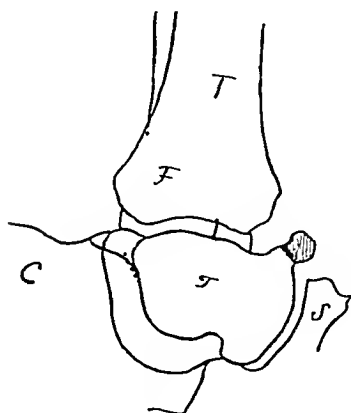


Fig 11—Trochlear process of the astragalus or possibly a fused secondary astragalus

The bone closely resembles a fracture of the internal malleolus. The inconstant bone may be bilaterally present, is smooth and regular and is to be ruled out as a cause of pain in traumatized ankles. We have seen one case in which a detached osteophytic process in a man suffering from osteo-arthritis of the ankle resembled very much an *os subtibiale*.

Fairbank has described an unusual epiphysis for the internal malleolus. All his cases have been in children (three cases, two bilateral). In one case he observed fusion of this bone three years after first observation. Whether or not this unusual epiphysis is the *os subtibiale* is not known. Lamberty and Beclard have also seen this anomaly. Both the *os subtibiale* and the epiphysis described are to be differentiated from a rare bone located at the posterior part of the sustentaculum tali, the *os proprium sustentaculi*.

The divided inner cuneiform, the divided cuboid as described by Blandin, and the *os intercuneiforme* have no functional significance. The secondary cuboid (*cuboides secundarius*), a bone located in the same general position as the *calcaneus secundarius* but in a more plantar and tibialward position may form a large bony projection in the sole of the foot as noted by Dwight in the foot of a cadaver. The clinical history was not known. Sutton, Thane, MacAlister, Blandin, Morestin, Gruber and Pfitzner have noted this bone in anatomic specimens. Holland, Bierman and Lilienfeld showed roentgenograms in which they thought the *cuboides secundarius* was visible. The *os unci* is present as a bony plantar projection on the third cuneiform and most probably cannot be felt. It is so rare in human beings (normal in cats) that one can only postulate that the enlarged process may be painful on walking. Lilienfeld believed that he saw it once. Holland noted that he observed an ossicle in the region of the peroneal process of the *os calcis* in relation to the external malleolus.

THE SESAMOIDS

It is not our purpose to discuss the anatomic, anthropologic and physiologic relations of the sesamoids of the foot. This would only lead us astray from a study of the functional derangements of these sesamoids. The reader is referred to the works of Pfitzner, Thilenius, Stieda, Gillette and others for such study.

Osteochondropathy of the sesamoids of the great toe, usually the tibial, is a clinical entity still resting on insecure ground. The etiology is unknown, a lowered resistance of the sesamoids toward mechanical damage in the period of greatest ossification being postulated. Increased static disturbances in a *pes planovalgus* has been noted in this condition. Meis, Remander, W. Muller and Treves have described cases. Osteochondropathy is usually found in children, often in association with other epiphyseal disease such as apophysitis of the heel, Kohler's dis-

ease of the second and third metatarsal head. A few cases have been noted in adults. Clinically, the symptoms are not characteristic—pain under the tibial sesamoid of the great toe, pain on motion of the great toe and on walking and, possibly, limping. Symptoms may not appear until late in the course of the disease. Roentgenologically, there is noticed fragmentation of the tibial sesamoid, usually in two irregular and unequal pieces. A tendency toward increasing fragmentation is seen. In Treves' patient, a girl aged 19, there was mottling of the tibial sesamoid, suggesting an osteochondritis. The bone was removed but not examined. Two pathologic specimens were examined by two investigators (Meis, Renander), who claimed that the typical picture of osteochondiopathy was present. Meis described the pathologic sequence thus—focal necroses of bone trabeculae and marrow, which become confluent, followed by a connective tissue reaction. The resulting frag-

TABLE 3—*Analysis of the Sesamoids of the Toes*

Division of the inner sesamoid of the great toe noted	72 times
Division of the outer sesamoid	6 times
Second tibial sesamoid noted	34 times
Second fibular sesamoid	Never seen
Third tibial sesamoid noted	4 times
Third fibular sesamoid	Never seen
Fourth tibial sesamoid noted	7 times
Fourth fibular sesamoid	Never seen
Fifth tibial sesamoid noted	163 times
Fifth fibular sesamoid noted	29 times
Interphalangeal sesamoid of the great toe noted	131 times

mentation leads to an appearance of pseudarthrosis. The hyaline cartilage covering remains undisturbed.

This condition is to be differentiated from congenital division of the sesamoids of the great toe and from fracture of these bones. Ossification of these sesamoids takes place about the eighth or ninth year, later according to some authors. Congenital division may be seen then. In our series of 1,000 roentgenograms, 72 showed division of the tibial sesamoid of the great toe and 6 showed division of the fibular sesamoid. Geist noted such division in 16 of 100 cases, Bizarro in 4 of 100, and Freiberg 1 in 1,000 roentgenograms. Hobart said that no case of division of the fibular sesamoid had ever been reported. The line of division may be transverse or oblique, the fragments being equal or unequal. The line of division is smooth. There may be division into four equal pieces. Sometimes, in addition to the main tibial or fibular sesamoid, one or two smaller sesamoids may be seen, imitating a congenital division. Muller noted that a swelling of the metatarsophalangeal joint may spread apart a congenitally divided sesamoid imitating fracture. Usually there are no symptoms but sometimes the patient may complain of pain on the under surface of the

great toe in the region of the tibial sesamoid. This most probably, is static, and relieved easily by proper conservative treatment. Bugman noted that in some cases of so-called congenital division, an old long-forgotten fracture of the sesamoid, sustained in childhood may be present.

Fracture of the sesamoids of the great toe is not common. Bizzaro having noted sixty cases up to 1921. Many authors have reported cases—Morian, Mouchet, Jean, Stulz and Fontaine, Hall-Edwards, Schunke, Marx, Hobart, Oll, Koch, Heinaman-Johnson, Muller, Speed, Skillern and Boardman, and others. It is unnecessary to make an analysis in each case to determine whether the condition is congenital division or a fracture. The fracture is usually the result of direct trauma, such as crushing or fall from a height, although some cases are due to indirect trauma. Experimentally, the fracture can be reproduced by forced dorsiflexion and abduction of the great toe. There may be associated fracture of the other bones of the foot, usually of the metatarsals and the phalanges. Fracture of the fibular sesamoid is much rarer, since the tibial sesamoid lies directly beneath the joint. Betocchi has noticed fracture of the fibular sesamoid in cases in which the sesamoid alone is involved by direct injury. Bizarro noted only six cases of fracture of the fibular sesamoid in his review of the literature. Clinically, there is pain under the affected sesamoid, increased on motion of the toe. A limp may be noticed. An association with hallux valgus is seen. On roentgen examination there is seen an unequal division of the affected sesamoid into more or less widely separated fragments, the line of division possibly being serrate. Roentgenograms should be taken with the toe in marked dorsiflexion, the rays being in the frontal plane after the technic of Muller. Treatment consists of rest, proper physical therapy and proper support. Callus unites the fractured ends, a fact which distinguishes it definitely from congenital division. In some cases it is necessary to remove the fractured bone. We are definitely in favor of conservative treatment. We have had cases in which operation was indicated for fracture relieved by paddings and plates. We have also noted that even after the removal of the affected sesamoid in some cases pain is still present but is easily relieved by proper support. Luxation of the sesamoids has also been described. This is not uncommonly noticed in marked hallux valgus in which condition the sesamoids are dislocated outward, the fibular sesamoid being seen in the first intermetatarsal space.

Arthritis of the sesamoids of the great toe is often seen especially in connection with arthritis of the joint of the great toe. The arthritic exostosis may be joined to a similar exostosis on the second metatarsal. Periostitis of the sesamoids may occur. We have not heard of osteomyelitis or tumor of the sesamoids of the great toe.

D J Morton described a backward displacement of the sesamoids of the great toe, and expressed the opinion that there is a definite static effect due to this malposition

Inconstant sesamoids at the heads of the metatarsals are seen at times We have never seen the fibular sesamoid on the second, third and fourth metatarsal heads Stieda described the fourth fibular sesamoid The tibial sesamoid on the fifth metatarsal head is common the fibular one less so Pfitzner's tables of frequency and combinations of the various sesamoids are very interesting Congenital division has never been described Pfitzner noted a division of the third fibular sesamoid in a tiger, the third tibial sesamoid being normal Recently, we noted a congenital division of the fibular sesamoid of the fifth toe into two parts We have also seen fracture of the second tibial sesamoid, the diagnosis being proved roentgenologically and by microscopic examination of the excised piece

CONCLUSION

The functional changes due to the inconstant bones of the foot and the sesamoids are not many but they become important in compensation work, especially in view of the fact that about 75 per cent of feet present such anomalies The inconstant bones seldom disturb the statics of the foot

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POSTOPERATIVE PULMONARY ATELECTASIS

OBSERVATIONS ON THE IMPORTANCE OF DIFFERENT TYPES OF BRONCHIAL SECRETION AND ANESTHESIA *

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The importance of pulmonary atelectasis as a postoperative complication has gained increasing recognition during the past few years. At first, attention was focused on the instances of massive collapse, as described by Pasteur¹ (1908) and again by Leopold,² who adopted Jackson's designation of "drowned lung," believing the condition to be best described as "post-operative massive pulmonary collapse and drowned lung." This condition is, of course, dramatic in all its phases, but is of relatively infrequent occurrence. However, so-called partial atelectasis is not uncommon—based on my own observations and those of many other observers. In fact, Mastics, Spittler and McNamee³ stated that the atelectasis accounts for about 70 per cent of all post-operative pulmonary complications.

Strictly speaking, the term partial atelectasis is incorrect. Atelectasis is complete in any given area, but is limited to a greater or lesser portion of the lung according to the magnitude or number of the bronchi that are obstructed. Thus the condition might be considered as "limited atelectasis." Therefore, it would seem advisable to drop the term "partial atelectasis" and to differentiate the various cases of atelectasis by terms descriptive of the areas of the lung involved. Lee and Tucker⁴ have offered a classification of the types of atelectasis noted, built on an anatomic basis, namely (1) massive atelectasis, (2) lobar atelectasis and (3) lobular atelectasis. To this I would add another group, viz., scattered lobular atelectasis, for the following reasons:

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¹ From the Clinics on Thoracic Surgery of the University of California (supported in part by the J J and Nettie Mack Foundation) and the Mount Zion Hospital

1 Pasteur William Massive Collapse of the Lung *Lancet* **2** 1351, 1902
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2 Leopold, Lewin S Postoperative Massive Pulmonary Collapse and Drowned Lung, *Am J M Sc* **167** 421 (March) 1924

3 Mastics, E A Spittler F Q and McNamee E P Postoperative Pulmonary Atelectasis *Arch Surg* **15** 155 (Aug) 1927

4 Lee Q E and Tucker G Postoperative Pulmonary Atelectasis, *Atlantic M J* **31** 284 (Feb) 1928

It is fairly well agreed that bronchial obstruction plus decreased aeration ability of the lung is a prime cause of postoperative pulmonary atelectasis, and that the obstruction is usually due to retained tracheobronchial secretions. Moreover, limitation of movement of the diaphragm for one cause or another (i. e., air below the diaphragm) greatly aids this process. Numerous other causes have been suggested without any general acceptance of any one of them.

It appears that the rôle of the bronchial secretions either in producing the atelectasis or in determining the specific type of atelectasis which ensues has not been given sufficient consideration. In a study of the action of cough on material in the tracheobronchial tract, Dr Archibald and myself⁵ observed that whereas the usual action of cough is to expel material from the tracheobronchial tree, it may, under certain conditions, actually bring about the opposite result, that is, drive material deeper. Moreover, it was noted that the degree of penetration of the material into the smaller ramifications of the tracheobronchial tree was in direct proportion to the viscosity of the material in question, that is, the less viscid the material, the greater was the penetration and the greater the possibility of dispersion.

In the cases of postoperative pulmonary atelectasis apparently due to bronchial obstruction by mucous secretion, I had the opportunity to observe carefully different types of secretion. The usual type of secretion consists of a thick viscid material, not necessarily present in large amounts, and broken up with difficulty. On bronchoscopic examination, this material is found to plug a bronchial orifice, atelectasis occurring distal to the plug. If the material is slightly less viscid one or more smaller bronchi may become plugged, and as the material found is again less viscid, smaller bronchi still are seen to be filled or plugged, and the possibility of obstruction in more than one bronchus increases. Finally, when one notes a secretion of almost watery consistency, then not only bronchial plugging, but also bronchial filling, may occur and one obtains clinically the condition which has been spoken of as "drowned lung" (Leopold²).

The experiments consisted in introducing intratracheally into animals, sputum that had been impregnated with iodized poppy seed oil 40 per cent, inducing controlled cough, and making roentgenographic observations. Thick, viscid sputum did not penetrate deeply, did not break up and was arrested at the orifices of the larger bronchi (fig. 1). Thin sputum (a sputum-iodized oil emulsion) penetrated deeply, filled the bronchi and was widely dispersed (fig. 2). In the various experiments all factors were identical except the type of sputum introduced.

⁵ Archibald E. and Brown A. L. Cough—Its Action on Material in the Tracheobronchial Tract. *Experimental Study*. Arch. Surg. **16**: 322 (Jan) 1928.

Clinically, I have frequently observed that thick, viscid sputum may plug larger bronchi and produce a postoperative lobular atelectasis. A typical case is reported (case 1, fig 3)

CASE 1—The diagnosis before bronchoscopy was atelectasis of a portion of the right lower lobe, after bronchoscopy, atelectasis of two tertiary lobules, right lower lobe

A 10 mm Bruning's bronchoscope was inserted. A small amount of thin mucous material was found in the trachea. The left primary bronchus was clear,



Fig 1 (cat 9)—In the cardiac region is seen an area of increased density corresponding to a mass of sputum-impregnated iodized oil, which had been injected intratracheally after cough had been induced. The mass is intact and has only penetrated the larger bronchi. Repeated induced coughs failed to disintegrate the mass or drive it further in.

no blocks were noted. At a distance of 37 cm from the mouth down the right primary bronchus and into the anterior secondary bronchus, two posterolateral tertiary bronchi were noted to have their orifices completely blocked by small plugs of thick tenacious sputum. The patient was asked to take deep breaths but these plugs were immovable, whereas the thin mucous secretion of the bronchi moved in and out with respiration. The entire area was sprayed with 10 per cent cocaine and 1:1000 solution of epinephrine equal parts. The aspirator was

applied directly to these plugs of mucus, and each was removed. The air was seen to enter the bronchi involved. The orifices of each were then touched with the mixture of cocaine and epinephrine, and before withdrawal were seen to be about one third larger than at the beginning of the procedure. After withdrawal of the bronchoscope, it was noted that the physical signs had changed, and that respiration was much easier.

Roentgenograms taken immediately before and after bronchoscopy showed clearing of the atelectatic area after bronchoscopy.

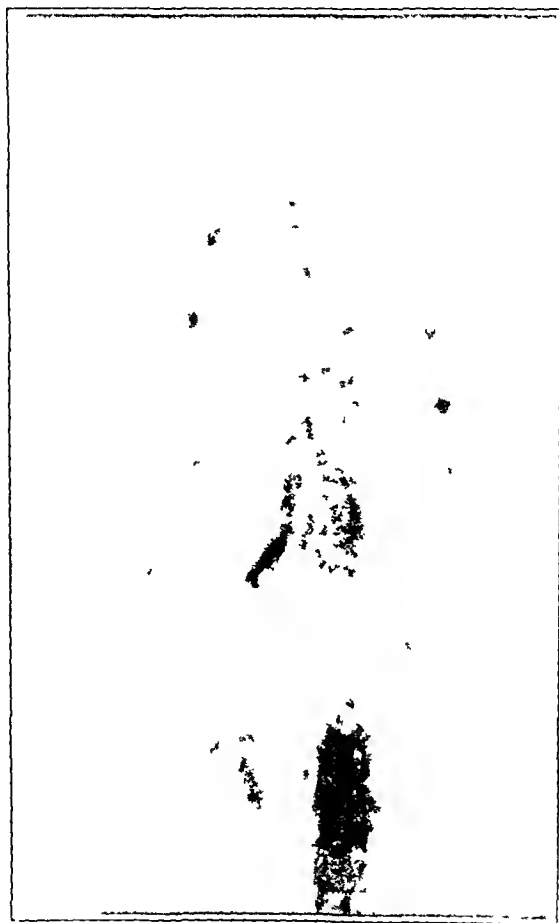


Fig 2 (cat 10) —After induced cough, sputum-iodized oil emulsion is seen dispersed and filling the larger and smaller bronchi.

Case 2 is a typical illustration of what may occur when the consistency of the sputum is much less viscid. In this case there was observed a dispersion effect with filling of numerous scattered bronchi and bronchioles. Directly comparable, it is believed, to the experimental observations previously reported.

CASE 2—The diagnosis before bronchoscopy was atelectasis of the right lung, after bronchoscopy atelectasis of the right lung and scattered atelectasis.

The large bronchoscope was inserted. About 30 cc of fairly tenacious sputum was aspirated from the trachea and primary bronchi especially on the right side.

No definite plugs were noted. The patient breathed more freely after the operation and was markedly improved symptomatically.

Roentgenograms taken immediately before and after bronchoscopy showed some clearing after bronchoscopic aspiration (fig 4). Roentgenograms taken twenty-four hours later showed marked clearing throughout.

Thus I have shown clinically that thick, tenacious sputum may plug a larger bronchus without interfering with the remainder of the tracheo-bronchial tree, and that a marked dispersion effect with filling of numerous widely scattered bronchi and bronchioles may occur when rather thin sputum is present. Intermediate degrees of dispersion and

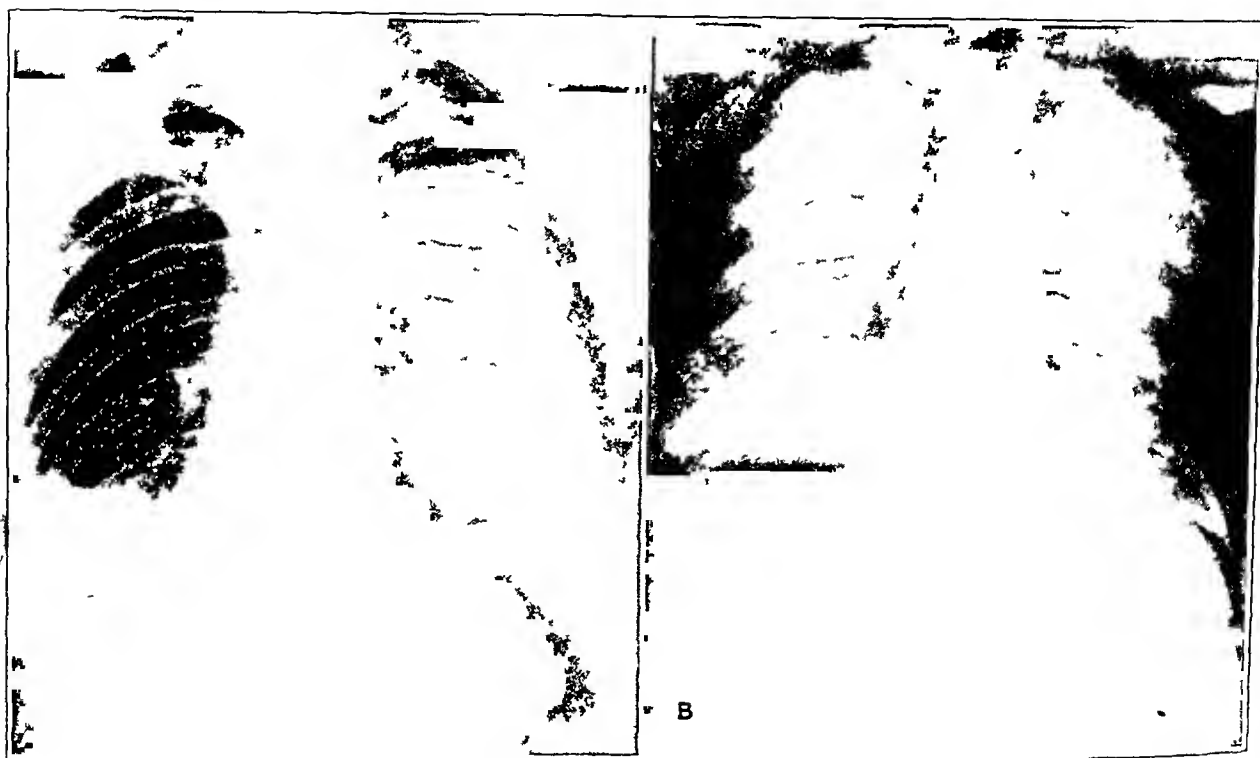


Fig 3 (case 1) — 4, roentgenogram taken immediately before bronchoscopy showing a triangular area of increased density at the base of the right lung. There was retraction of the ribs on the right and the heart and mediastinal contents were drawn slightly toward the right. At bronchoscopy, the bronchus in this area of increased density was found to be occluded by a thick tenacious plug. *B*, taken after bronchoscopy showing marked clearing of the triangular shadow at the base of the right lung and widening of the interspaces. The heart and mediastinal contents have swung back toward the left. This followed the bronchoscopic removal of the thick tenacious mucous plug filling the bronchus to the area involved.

plugging of a few or many bronchi in other clinical examples were obviously to be expected and this has been noted repeatedly, the cases quoted herewith fall respectively toward each end of the scale.

INFLUENCE OF TYPE OF ANESTHESIA

It has been my privilege to observe the course of postoperative pulmonary complications following practically all types of anesthetics. The majority of the operations were performed under subarachnoid block. Likewise, the greatest number of cases in which postoperative pulmonary atelectasis were observed were those in which spinal anesthesia had been employed. While the series is numerically too small to give definite statistics for the incidence of this complication following the various types of anesthesia, nevertheless, the impression gained thus far is definitely that the incidence of pulmonary atelectasis is greater follow-



Fig 4 (case 2) — *A*, roentgenogram taken before bronchoscopy showing diffuse scattered areas of increased density throughout both lobes. At bronchoscopy, a large amount of semiviscid material was found in all the major bronchi. *B*, after bronchoscopy, during which procedure 30 cc of semiviscid material was aspirated from the primary bronchi, showing slight general clearing most marked on the right.

ing spinal anesthesia than following any form of inhalation or regional anesthetic. This impression holds regardless of the type of operation undertaken.

At first thought one would imagine the opposite to be true, that postoperative pulmonary atelectasis would occur more frequently following inhalation anesthesia. But on closer consideration several reasons are noted why spinal anesthesia might predispose to this complication.

First, spinal anesthesia definitely inhibits the depth and force of respiratory movements, not only during the operation itself, but for a considerable period thereafter. It is these respiratory movements (both intrinsic and extrinsic) which tend to rid the tracheobronchial tree of foreign matter or secretions. Second, the normal viscosity of the secretions of the tracheobronchial tree appears to be increased, i. e., the material is more tenacious following spinal anesthesia. Third, following operation under spinal anesthesia the patient tends to remain relatively quiet for a number of hours. One has, then, a more tenacious sputum and decreased or impaired factors that might tend to free the tracheobronchial tree of this material. The increased possibility for this material to obstruct or plug a bronchus and the subsequent development of atelectasis appear reasonable.

SUMMARY

1 The importance of the bronchial secretions in producing post-operative atelectasis and in determining the specific type of atelectasis which ensues is stressed. Experimental and clinical observations are compared, and are found to agree. Thick tenacious sputum is noted to plug the larger bronchi, whereas thinner sputum tends to greater dispersion and a blocking of the finer bronchi and bronchioles, thereby producing a scattered lobular atelectasis.

2 The impression is gained that spinal anesthesia predisposes to postoperative pulmonary atelectasis.

GASEOUS PERICHOLECYSTITIS WITH CHOLECYSTITIS AND CHOLELITHIASIS

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Gas bacillus infection of the liver and biliary tract has been reported many times. In a perusal of the available literature, I have not found a case in which gas formation around the gallbladder was noted during life. Kuchmayr reported an interesting case of gas bacillus infection within the gallbladder, the walls of which showed emphysematous blebs.¹

In the case presented, gas in increasing volume was demonstrated both clinically and roentgenologically in relation to the gallbladder. The gas present at the time of operation was proved by culture to be due to an unusual gas bacillus resembling the *Bacillus welchii*.²

In all case reports of emphysema of the liver, the presence of gas was first noted post mortem. It is interesting that invariably there was an associated chronic cholangitis, usually with cholelithiasis.

From a microscopic study of the liver and biliary system in cases of "Schaumleber," Stolz³ concluded that the invasion of the bile ducts and gallbladder by the gas bacillus was terminal and the gas formation a postmortem feature. Hirtze,⁴ Kerschensteiner,⁵ Welch - and others are of the opinion that the invasion and localization of gas producers in the bile ducts and periacinal areas of the liver may occur during life; the production of gas begins only after cessation of the circulation.

Bacillus aerogenes-capsulatus is frequently present in the bowel. It may be present in the circulation without causing symptoms until some intercurrent necrotic or inflammatory lesion develops which forms a favorable nidus for its growth. A necrotic area being deprived of or limited in its supply of well oxygenated blood may determine such localization.

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From the University of Colorado School of Medicine and Hospitals

² Read before the Western Surgical Association, Del Monte Caln Dec 13 1929

1 Kirchmayr Centrbl f Chir 52 1522 1925

2 Welch W H and Nuttall C H F Bull Johns Hopkins Hosp 3 81 1891

3 Stolz Arch f Path 165 90 1901

4 Hirtze Munchen med Wchnschr 1895 no 10 p 290

5 Kerschensteiner Deutsches Arch i klin Med 69 38 1900

The liver eliminates bacteria from the general and the portal circulation through the biliary ducts⁶. This function is of prime importance for the maintenance of health. It may become an equally important etiologic factor in diseases of the hepatic system. Investigations by different observers show that a variety of bacteria may be present in the liver and bile for an indefinite period without clinical manifestations of their presence. The liver and bile must possess the power to modify or control the virulence of bacteria.

An increase in alkalinity of the bile has a marked inhibitory and possibly a bactericidal effect⁷. This may explain why bile may be sterile, whereas the walls of the gallbladder and biliary ducts with the pericystic and periductal fibrous tissues and the contiguous liver cells retain and manifest bacterial infection.

Any severe or fatal illness which diminishes the secretion or alters the character of bile, any condition reducing the contractility of the gallbladder⁸ or which causes biliary stasis,⁹ favors infection of the bile. These factors can be held to account for descending as well as for ascending biliary infection.

The routes of infection to the gallbladder and bile passages have recently attracted renewed attention of investigators, notably Graham¹⁰ and his co-workers, Peterman and Priest¹¹. It is important to know the route of invasion in order to understand diseases of the hepatic system. Usually when the patient with hepatic disease seeks medical aid, the avenues of invasion are so intimately and inseparably associated that the disease is presented as an overlapping and confusing pathologic complex.

Systemic infection with gas producers may follow even minor injuries to the surfaces of the body, or minute or massive perforations of the hollow viscera. Lesions of the bowels, ulcers, contusions, strangulation or obstruction which increase permeability of the wall without solution of continuity may be the site of inoculation. There may be no visible point of inoculation¹². Gas bacillus infection of the gastrointestinal tract and related systems is usually an autoinfection.

The routes of invasion of the gallbladder and bile passages may be

6 Futterer. *Berl klin Wchnschr* 36 58, 1899

7 Beckmann, K. *Munchen med Wchnschr* 75 2042 1928

8 Gilbert and Gironde. *Centralbl f Bact* 9 413, 1891

9 Ehret and Stolz. *Mitt u d Grenzgeb d Med u Chir* 7 8, 1901

10 Graham, E. A. *Surg Gynec Obst* 26 521, 1918

11 Peterman M. G., Priest, W. S., and Graham, E. A. The Association of Hepatitis with Experimental Cholecystitis and Its Bearing on the Pathogenesis of Cholecystitis in the Human, *Arch Surg* 2 92 (Jan) 1921

12 Welch, W. H. and Flexner, S. *J Exper Med* 1 5 1896

(a) Arterial A part of a general sepsis,¹³ from remote foci, as proved by the work of Rosenow,¹⁴ bacterial emboli in the subepithelial or submucous tissue of the gallbladder¹⁵

(b) Venous Thrombophlebitis, thrombosis of the portal vein or its branches a result of filtration of bacteria from the general, splenic or portal circulation by the liver cells through bile ducts¹⁶

(c) Lymphatic From the liver, from organs contiguous to or in physiologic relation with the liver Graham¹¹ showed the lymphatic route as probably the most frequent, corroborating the studies of other workers who found the greatest and most constant evidence of infection in the periportal, periductal and perivesicular fibrous tissues, which conduct the lymphatic channels

(d) Adhesions between the bowel, liver and gallbladder Adhesions, primarily a protective inflammatory reaction, become a bridge across which infections may travel in both directions The same features obtain between the undersurface of the liver, the sulcus of the gallbladder and the gallbladder proper

(e) Direct extension from the liver by continuity

(f) Bile stream infection Ascending from the duodenum, descending from the hepatic ducts

REPORT OF CASE

History—J B L, a man, aged 62, was admitted as an ambulant patient to the medical service of Dr C T Burnett on March 21, 1929, complaining of pain in the upper part of the abdomen He had had a similar attack of three hours' duration three weeks before, otherwise he was well Five days before admission, following a heavy meal, he was seized with sudden agonizing pain in the upper right quadrant of the abdomen The pain radiated to the back and to the right shoulder, and persisted for four and one-half days He was nauseated and vomited undigested food and bile Jaundice was noted on the second day, which began to fade on the day before admission

Examination—On physical examination the patient was found to be robust and did not appear ill The temperature was 99 F, the pulse rate 92 and the respiratory rate 22 The skin and sclera were jaundiced The right upper quadrant of the abdomen was rigid and tender below the right costal border No mass was palpable The heart was normal The systolic blood pressure was 136 and the diastolic 76 The blood count was red blood cells, 4,910,000, white blood cells, 14,100, polymorphonuclears, 90 per cent, small lymphocytes, 10 per cent The Wassermann reaction was negative The urine was hazy, with acid, albumin, 1 plus, no sugar and an occasional hyaline cast

March 23 The patient was up and about and felt well The gallbladder visualization test was done with the dye administered intravenously The area of gas in the region of the gallbladder was shaped like a gallbladder, but the organ

13 Moynihan, B Brit M J 1 1, 1928

14 Rosenow, E C Mayo Clin 8 222, 1916

15 Koch Ztschr f Hyg u Infektionskr 72 1 1909

16 Pesch, K L, and Hoffmann, V Munchen med Wchnschr 75 1705, 1928

itself failed to visualize after twelve hours Dr J L Harvey made the diagnosis of a pathologic gallbladder

March 24 A surgical consultation was held Slight icteric conjunctiva, slight tenderness of the abdomen over an enlarged liver, and slight rigidity of the abdominal wall to about the center of the abdomen were noted Operation was advised

March 25 The patient was comfortable The temperature was 99 F, the pulse rate 86 and the respiratory rate 18 The abdominal rigidity was less

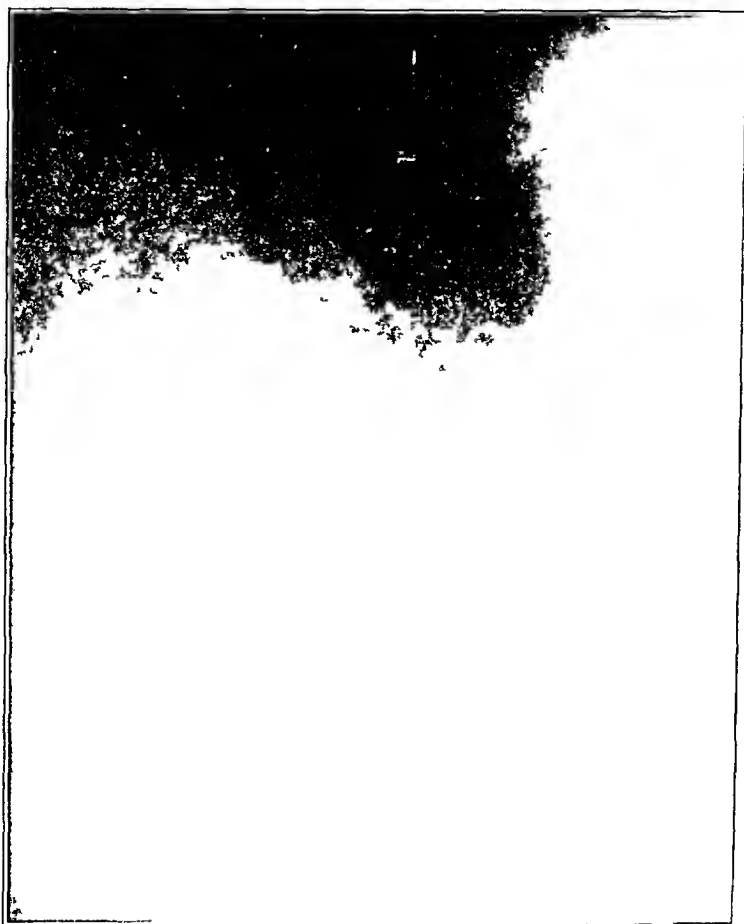


Fig 1—March 23 1929 The visualization test was made with dye administered intravenously The area of gas in the region of the gallbladder was shaped like a gallbladder, but the organ failed to visualize Note the mottling of gas in the area of the pericystic region

marked A tumor mass in the region of the gallbladder could be felt to extend below the margin of the liver It was tender to light palpation and tympanic to percussion A gastro-intestinal series was requested to determine the origin of the air in the gallbladder and to note a communication, if any, with the gastro-intestinal tract

March 26 A gastro-intestinal series showed persistent deformity of the duodenal cap which was small irregular and difficult to visualize Gas pre-

viously described in the area of the gallbladder on the visualization test had increased in size. It was not connected with the bowel, the fluid level was seen with the patient in an erect posture.

March 27. The patient was transferred to the surgical service. The temperature was 99.8 F, the pulse rate 96 and the respiratory rate 22. The mass was greatly increased in size and was quite tender on palpation and tympanic on percussion.



Fig. 2—March 25, 1929. There is a great increase in the gaseous area in the gallbladder region to four times the size shown in figure 1.

Operation—The operation was performed with the patient under ether anesthesia. The usual gallbladder incision was made, and the peritoneum opened. The colon, omentum, duodenum and stomach were firmly and intimately adherent to the margin of the liver and region of the gallbladder, making a mass the size of a large fist. It was tympanic, the gas was under considerable tension. The adhesions were separated causing a great amount of bleeding, but the oozing area was packed with hot compresses. The tumor mass was very friable. A number of small abscesses were found in the wall. The outline of the gallbladder was very indistinct. When an attempt was made to find a line of cleavage, the hemorrhage became profuse, but was controlled by hot compresses. It was

deemed expedient merely to drain the gallbladder. A 20 cc syringe with 19 gage needle was thrust into the tumor, the gas was under sufficient tension to push the plunger out of the barrel of the syringe. Cultures were taken by Dr Ivan Hall. Coffer-damming strips were used over the entire area. On carrying the strips high up under the surface of the liver, a tear was made in the tumor mass, or a secondary abscess, with escape of rice-soup-like fluid. No odor was noticed. A large tube was introduced into the tip of the tumor. It could not be sutured because of the friability of the tissue. Bleeding was profuse. The finger was introduced into the cavity, supposedly the gallbladder, but no stones were felt. The cavity was filled with thin, bloody fluid, free and clotted blood. No bile was seen. A larger tube was inserted and deep mattress suture succeeded in stopping the bleeding and holding the tube. The tube, the coffer-damming strips of gauze and the protective rubber-dam were brought out through the abdominal incision, which was only partially closed. The patient left the operating table in good condition.

Course—During the afternoon, the drainage of a thick greenish fluid was profuse, 500 cc was caught in a syphon bottle. The dressings were saturated and had to be changed several times.

March 28 The temperature was 100 F and the pulse rate 120. The patient's general condition was good. There was profuse drainage of thick, greenish fluid, the abdomen was not distended and no odor was noticed. No crepitus was felt in the abdominal wall. The patient took fluids freely. He voided voluntarily and passed flatus. Twenty cubic centimeters of Cutter's polyvalent anaerobic serum was given intramuscularly.

March 29 The temperature was 99 F and the pulse rate 114. No crepitus was noted in the tissues. There was free drainage of bile-stained fluid. Twenty cubic centimeters of polyvalent serum was given intramuscularly.

March 30 The temperature was 99.2 F and the pulse rate 108. The patient was comfortable and in no pain. There was profuse drainage of clear bile-stained fluid. No crepitus was noted in the tissues. Twenty cubic centimeters of polyvalent serum was given intramuscularly.

March 31 The temperature was 98 F, the pulse rate 94 and the respiratory rate 26. About 8:20 a. m., while on the bedpan straining at the stool, the patient was suddenly seized with severe respiratory distress and became cyanotic. I happened to walk into his room when this occurred. He did not complain of pain, only of the extreme breathlessness. Examination of the lungs gave negative results. Oxygen inhalations gave no relief. At 9:35 a. m., while straining at the stool, he died.

Abstract of the Autopsy Report (Dr W. C. Johnson)—Autopsy was performed three hours post mortem. The anatomic diagnosis was suppurative pericholecystitis, cholelithiasis, necrosis with perforation of the neck of the gallbladder, slight biliary cirrhosis of the liver, chronic inflammation and fibrosis of the liver adjacent to the gallbladder, thrombosis of the external and internal iliac veins and pulmonary embolism, the cause of death.

The heart was enlarged. The right ventricle and pulmonary artery opened in situ contained a mass of firm, dark red cylindric and branching thrombi, which extended into the branches of the pulmonary artery.

Examination of the abdomen showed no general peritonitis and no gaseous emphysema. The region of the operative field was well walled off by fibrinous adhesions, forming a pocket into which a rubber sheet drain surrounding a

number of gauze strips extended from a laparotomy wound. A rubber tube drain was sutured into an opening through a layer of tissue which completely covered the region of the gallbladder.

The liver weighed 2,530 Gm. The capsule was thickened, and there was slight biliary cirrhosis. The gallbladder region was covered by a layer of fibrous tissue on the outer surface of which was a fibrinous exudate. A rubber tube drain was sutured in an opening through this tissue near the edge of the liver. An incision through the liver into this region revealed the gallbladder free and collapsed in the apex of a pear-shaped abscess cavity, where it was attached to the cystic duct. Near the neck of the gallbladder was a perforation 1 by 2 cm. through which had been extruded the mulberry-shaped calculus found lying free in the apex of the abscess cavity. The collapsed, slightly thickened, gallbladder wall, roughened on its external surface, contained twelve faceted calculi. The mucosa of the gallbladder appeared practically normal. The wall of the abscess cavity which completely enclosed the gallbladder was made up of fibrous tissue lined with granulation tissue. Several hummocks of granulation tissue projected from the liver into the abscess cavity, causing an irregular contour. On the left side of the gallbladder fossa a layer of fibrous tissue extended for 2 cm. into the liver substance, forming an abscess which communicated with the main pericholecystic abscess cavity.

Microscopic Examination—The liver showed a slight increase of connective tissue in the portal canals. This tissue was infiltrated with lymphocytes, very marked in some places. The bile ducts appeared normal.

The fossa of the gallbladder was lined by a layer of exudate containing leukocytes, fibrin and masses of yellow pigment. This exudate rested on a layer of granulation tissue, beneath which was a layer of fibrous tissue from which bands of fibrous tissue extended deeply into the adjacent liver tissue.

The gallbladder showed complete loss of nuclear stain. The outline of the layers of the wall could be distinguished. The mucosa and muscularis showed no thickening or infiltration. The outer coat was thickened and studded with masses of granular yellow bile pigment. Sections stained for bacteria showed very few long filamentous, gram-negative organisms in the outer coat.

Abstract of the Bacteriologic Report (Ivan Hall, Ph.D.)—Two specimens were taken from the field of operation.

The specimen from the blood around the tumor mass, after the surrounding adhesions were separated, showed a pure culture of an atypical *Bacillus welchii*.¹² The specimen from the cavity proper also showed atypical *Bacillus welchii* in pure culture. Ten cubic centimeters of blood from the median basilic vein three hours after operation was negative on culture.

Bacteriologic culture studies at autopsy revealed the heart blood to be normal and the bile showed gram-positive filaments and rods resembling those isolated at the time of operation. Three varieties of staphylococcus were isolated: *Micrococcus aureus*, *Micrococcus antiaerius*, *Micrococcus epidermidis* and *Bacillus tetius*.

The Cutter's triple anaerobic serum contains in each cubic centimeter 5,000 guinea-pig minimum lethal doses of *Bacillus oedematiens* (*Bacillus novyi*) toxin, 300 rabbit minimum lethal doses of *Bacillus welchii*.

This serum is similar to that developed by Weinberg¹⁷ and used by the French in cases of gas gangrene during the World War.

17 Henry, Herbert, and Lacey, Margaret. J. Path. & Bact. 23: 283, 1920.

COMMENT

There was cholecystitis with cholelithiasis of considerable duration. The patient's first attack of biliary colic three weeks before admission to the hospital may have inaugurated the incarceration of the mulberry calculus which was found at autopsy ulcerated through the wall at the neck of the gallbladder.

The walls of the gallbladder on microscopic study disclosed pathologic changes extending from the necrotic mucosa to the thickened pericholecystic fibrous tissue. The gallbladder was entirely separated from the liver and the enveloping bridge of fibrous tissue.

The infection was of longest duration and of greatest intensity in that portion of the pericholecystic cavity corresponding to the sulcus for the gallbladder. This is evidenced by the microscopic slides and the small abscess deep in the liver margin of the sulcus.

It is improbable that the infection was hematogenous, since the blood cultures both ante and post mortem were negative, further there was no gaseous emphysema elsewhere before or after death. Consideration must be given to the effect of the triple anaerobic serum which may have controlled whatever blood infection may have been present.

Ascending or descending infection via the bile to the gallbladder seems improbable, because the mulberry calculus blocked the cystic duct until it ulcerated through the neck of the gallbladder. When this occurred cannot be conjectured. This necrotic area furnished a favorable nidus for localization and growth of the gas bacillus. Intracholecystic accumulation of gas may have been a factor in the extrusion of the calculus. The abscess cavity must have been developed before the extrusion.

Extension from the gallbladder is a possibility, but the microscopic studies are not suggestive.

Most likely the gas bacillus was an auto-infection extending directly from the liver or indirectly from the liver to the perivesicular tissue, the primary extension being across the bridge of adhesions between the bowels, stomach, duodenum and colon and the under surface of the liver. As the gallbladder was completely enveloped up to the cystic duct by a preformed, well developed fibrous tissue, adhesions were prevented from forming between the gallbladder and other viscera, excluding direct extension to the gallbladder.

The intramuscular injection of the triple anaerobic serum (Cutter) seems to have had a favorable influence in controlling the gas bacillus infection.

The postoperative course was remarkably smooth with no extension of the gaseous emphysema until the pulmonary embolus developed causing death on the fourth postoperative day.

PRIMARY, ISOLATED LYMPHOGRANULOMATOSIS OF THE STOMACH *

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Ever since the time of Billroth, Hodgkin's disease, by general agreement, has been excluded from the category of surgical diseases. The reason for considering the disease as nonsurgical was due not so much to the technical difficulties entailed as to the unfavorable end-results. The fact that pathologists subsequently demonstrated that the disease might begin as an isolated lesion did not alter the surgical status of the disease. Appraisal of the occurrence of isolated lesions failed to modify previous opinion, because the organs described as the seats of primary involvement, such as the spleen, the liver, the bone-marrow and the lungs, either did not lend themselves to surgical extirpation or did not lead to clinical manifestations that might have permitted early recognition. In the past few years, a number of patients with isolated lymphogranulomatosis of the gastro-intestinal tract have been treated by radical resection, generally under a mistaken clinical diagnosis. The results obtained in these cases are sufficiently favorable to challenge the prevailing *noli-me-tangere* policy and to call for a reconsideration of the question. Of particular interest, especially in connection with the case here reported, are the isolated lesions of the stomach, the phase of the subject with which this paper will mainly deal. For a summary of the primary and limited intestinal cases, the reader is referred to Goedel,¹ Slovacek,² Pissarewa,³ and the splendid article of Coronini.⁴

The first case of strictly isolated lymphogranulomatosis of the stomach was reported by Steindl,⁵ in 1924. The preoperative diagnosis was gastric carcinoma. At operation an infiltrating tumor, involving

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1 Goedel, A. Zur Kenntnis des primären, isolierten Darmlymphogranuloms, *Wien klin Wchnschr* **42** 426 (April 4) 1929

2 Slovacek, O. Príspevek k lymfogranulomatóse zezivacého traktu, *Časop lek česk* **68** 503 (April 5) 1929

3 Pissarewa, T. Lymphogranulomatosis (Paltauf-Sternberg) des Verdauungstraktes, *Arch f klin Chir* **149** 75 (Dec) 1927

4 Coronini, C. Ueber das Paltauf-Sternberg'sche Lymphogranulom, *Beitr z path Anat u z allg Path* **80** 405, 1928

5 Steindl, H. Ueber einen Fall von Lymphogranulomatose des Magens, *Arch f klin Chir* **130** 110 (April) 1924

the pyloric and prepyloric regions, was found, together with a number of glands the size of a hazelnut in the adjacent lesser omentum and in the gastrocolic ligament. Exploration of the remainder of the abdominal organs failed to disclose other lesions. A resection was performed, and the patient made an uneventful recovery. Postoperative observation over a period of a year yielded no evidence of recurrence or development of other foci. Later in the same year, Neuber⁶ presented before the Eleventh Hungarian Surgical Congress a case of isolated Hodgkin's disease that was clinically diagnosed as ulcer. Partial gastric resection led to the discovery that the lesion was lymphogranulomatous. In 1926, a case similar to that of Steindl was observed in South Manchuria by Kan.⁷ A woman, aged 52, was operated on for a suspected carcinoma, and a gastric tumor and three glands the size of a pea were resected. The growth, when examined microscopically, proved to be Hodgkin's granuloma. The postoperative course was uneventful for a month, when persistent vomiting set in and led to death. Autopsy disclosed an obstruction at the site of the anastomosis and, in addition, lesions that were diagnosed as those of an old case of tuberculosis of the apical and cervical glands. No other morbid processes were noted grossly.

In May, 1926, von Redwitz⁸ presented a case before the Surgical Society of Munich, in which the preoperative diagnosis was peptic ulcer. The pyloric lesion encountered at operation led to a suspicion of carcinoma and occasioned a resection. The histologic diagnosis of the surgical specimen was lymphogranulomatosis. The following year (1927) a detailed report was published by Thieme⁹ dealing with a case of isolated gastro-intestinal lymphogranulomatosis observed at the clinic of von Redwitz. Presumably, the reports of both authors refer to the same case. The histologic appearance of Hodgkin's disease in the case of Redwitz and Thieme was complicated by the presence of numerous foreign bodies and foreign-body giant cells. Further difficulty in the elucidation of the origin of the disease resulted from the circumstance that a month prior to admission the patient had drunk hydrochloric acid. Following recovery from the operation, the patient left the hospital and did not return for observation. In 1927,

6 Neuber, E. Magengranulomatose, Zentralorg f d ges Chir u ihre Grenzgeb **31** 309 1925

7 Kan, J. N. Report on a Case of Lymphogranuloma in the Stomach, J Orient Med **5** 9 (July) 1926

8 von Redwitz, E. Vereinigung Munchener Chirurgen, Zentralbl f Chir **53** 2087 (Aug 14) 1926

9 Thieme, P. H. Zur Kasuistik der isolierten Lymphogranulomatose des Magendarmtraktes, Deutsche Ztschr f Chir **205** 404 (Sept) 1927

Froboese¹⁰ described a case in a woman, aged 63, in whom a prepyloric tumor and slightly enlarged lesser omental glands were resected for supposed carcinoma. The microscopic diagnosis was Hodgkin's granuloma. Following convalescence, further search for evidence of other lymphogranulomatous foci yielded negative results.

An interesting case observed by Vasilu¹¹ in 1926 and reported in 1929 was that of a medical student who was thought to be suffering from a gastric ulcer. Failure of response to medical treatment led to a partial resection of the stomach and extirpation of the glands along the lesser curvature, one of which was the size of a walnut. After recovering from the operation, the patient was able to finish her medical course without physical handicap, and she was still well when Vasilu's manuscript was submitted for publication. Other cases, such as those of Gossman and of Lubarsch,¹² which are referred to at times as isolated gastric Hodgkin's disease, but in which limitation to the stomach is questionable, are best omitted from the category of strictly isolated cases.

There are a number of cases reported, besides those cited, in which the lymphogranulomatosis was localized to the gastric region but not strictly limited to the stomach and the perigastric lymph glands. The case described by Scott and Forman¹³ can be designated as regional in that the disease, although not limited to the stomach, had not spread beyond the contiguous structures. According to these authors, the lymphogranulomatosis led to a shrinking and a thickening that extended from the pylorus to from 3 to 5 cm beyond the cardia into the esophagus. The wall of the stomach was adherent to the upper pole of the spleen and to the diaphragm. The perigastric and peripancreatic glands were enlarged. There was no further evidence of overgrowth elsewhere, either in the lymph nodes or in the mucous membranes. Hayden and Apfelbach¹⁴ reported three cases of gastro-intestinal lymphogranulomatosis, in one of which the disease was localized to the stomach and its vicinity. In a second case there was an associated involvement of

10 Froboese, C. Bemerkungen an der Hand eines Falles von Lymphogranulom des Magens, Beitr z path Anat u z allg Path **77** 363 (April) 1927.

11 Vasilu, T. L'ulcere lymphogranulomateux gastroduodenal, Sang **3** 257 1929.

12 Lubarsch, quoted by Konjetzny, G. E. Die Entzündung des Magens. Lymphogranulomatose, in Henke F, and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1928, vol 4, part 2, p 1060.

13 Scott, E, and Forman, J. Lymphoblastomata of the Gastrointestinal Tract. With a Report of a Case of Hodgkin's Disease of the Stomach, Ohio State M J **12** 323 (May) 1916.

14 Hayden H. C. and Apfelbach, C. W. Gastro-Intestinal Lymphogranulomatosis Arch Path **4** 743 (Nov.) 1927.

the lower mediastinal lymph glands. In the case reported by Sussig,¹⁵ in a man, aged 42, the primary lesions was located in the pars media on the lesser curvature of the stomach and adherent to the pancreas and the liver. The mesocolon and the root of the mesentery were infiltrated, and the perigastric, periaortic and peripancreatic lymph glands were enlarged. The reason for separating the regional from the strictly isolated cases is that the former are too extensive for surgical extirpation.

A great deal of circumspection is necessary before a case of gastrointestinal lymphogranulomatosis can be considered as strictly isolated. Gross lesions may be present in organs inaccessible to the surgeon who performs the operation and, therefore, they may be entirely overlooked. Pissarewa³ mentioned a case observed by Pokotilo and Busni, in which a lymphogranulomatous cecum was the only lesion discovered at operation. Postmortem examination disclosed a solitary granulomatous node in the spleen. In case 2 reported by Vasilu,¹¹ in which a gastric resection for Hodgkin's granuloma had been performed eight hours antemortem, the autopsy likewise revealed a small nodule in the spleen. Even an autopsy does not insure the discovery of lesions outside of the digestive tract unless a microscopic search is instituted. In a case of diffuse lymphogranulomatosis of the intestinal tract with perforation of the jejunum, recorded by Warfield and Kristjansen,¹⁶ the splenic and hepatic involvement was a microscopic revelation. The generalized nature of the process in the case of Bianchi,¹⁷ in which the principal gross changes were localized in the stomach, was detected by histologic means. Under exceptional circumstances, even the most painstaking gross and microscopic examination may be insufficient to discover the primary source, as in the case described by Sternberg.¹⁸ This author cited an instance of gastric lymphogranulomatosis in a person who, six years prior to death, was treated by roentgen rays for a large mediastinal tumor. No remnant of the growth which, according to Sternberg, indubitably represented granulomatous glands could be identified at autopsy.

The case here reported is unique in the literature on lymphogranulomatosis of the stomach in that it is the only one so far as could be ascertained, in which a careful clinical history and a gross and microscopic study of the tissues obtained at necropsy showed that the disease was limited to the stomach and the perigastric lymph glands. The other

15 Sussig, L. Sul linfogranuloma maligno dello stomaco, *Pathologica* **21** 397 (Aug 15) 1929.

16 Warfield, L. and Kristjansen, H. T. Hodgkin's Disease of the Intestines with Report of a Case, *Bull. Johns Hopkins Hosp.* **27** 24 (Jan.) 1916.

17 Bianchi, A. E. Granulomatosis, *Semana med.* **1** 432 (March 16) 1922.

18 Sternberg, C. Die Lymphogranulomatose, *Klin. Wchnschr.* **4** 529 (March 19) 1925.

cases of isolated Hodgkin's disease referred to were, with the exception of Kan's,⁷ surgical cases in which operation was followed by recovery, and examination of other tissues was therefore precluded. In Kan's case an autopsy was performed, but a complete microscopic study was not made post mortem, at least so far as can be determined from the rather complete summary of the case in English.

CASE REPORT

M. G., a white man, aged 62, who first entered the Cook County Hospital on June 30, 1928, stated that in October, 1926, he began to notice a burning pain in the left hypochondrium, it appeared regularly at 4 p. m. and lasted until the evening meal. On account of this distress cholecystectomy and appendectomy were performed in May, 1927. Subsequent to the operation, the pain appeared following each meal, usually after an interval of from one-half to four hours. Eructations of acid were particularly prominent in the afternoon. The ingestion of soda was tried a number of times, but it failed to afford relief. The effect of food on the pain had not been tested. At the age of 28 the patient had suffered from post-prandial, epigastric burning of one month's duration. Tablets prescribed by a physician appeared to check the attack. The patient remained well for five years, then he suffered from an excruciating knifelike pain in the epigastrium, which required morphine for relief. A similar attack occurred five years later, at the age of 38. In 1912, a brief siege of "water-brash" of two months' duration, unassociated with pain, was experienced. From that time until October, 1926, the patient had no complaints. Aside from loss of appetite of six months' duration and a loss of 30 pounds (13.6 Kg.) during the eighteen months of illness, a general inventory of symptoms afforded no significant information.

The temperature and the pulse and respiratory rates were normal. The blood pressure was 138 systolic and 72 diastolic. Except for the presence of a scar on the right upper quadrant, abdominal examination gave negative results. Examination of the blood revealed hemoglobin, 60 per cent, erythrocytes, 3,330,000, white blood cells, 7,600, of which 76 per cent were neutrophilic leukocytes, 20 per cent lymphocytes and 4 per cent monocytes. The Ewald meal yielded 60 cc. with 45 per cent free and 18 per cent combined acidity. Of four stools passed on successive days, the first two gave a positive and the second two a negative test for occult blood. The Wassermann reaction of the blood was negative. A roentgenogram of the stomach (fig. 1) demonstrated a constant shallow irregularity on the lesser curvature in the prepyloric area, opposite which was an incisura. Projecting from the proximal margin of the incisura was a persistent niche. The roentgen diagnosis was indeterminate.

The patient improved steadily on Sippy management, but the response was neither as rapid nor as complete as is usual in cases of uncomplicated ulcer. The patient left the hospital on July 30, 1928, with instructions to report to the gastrointestinal follow-up clinic. At his first visit to the clinic on August 2, he weighed 144 pounds (65.3 Kg.). He was placed under ambulatory management for ulcer and was permitted to return to his occupation. He gained weight and strength and except for slight pain that could be controlled by returning to a strict regimen he felt well. He visited the clinic last on July 18, 1929, when he weighed 161 pounds (73 Kg.) and stated that he was having no pain.

The patient reentered the hospital on March 18, 1930, asserting that following discharge in July, 1928, he remained relatively symptom-free for three months.

After that time the previous burning pain returned at irregular intervals, but it was merely diurnal and remained amenable to treatment. Three months prior to his second admission, in December, 1929, he began to suffer from pain at night, and six weeks later the epigastric burning became almost continuous. The alkaline powders, according to the patient, served as "kindling for the internal fire" during the latter stage. Vomiting after the ingestion of food, which previously occurred occasionally, now appeared almost daily. Emesis afforded only partial relief. Within the last few weeks complete anorexia had appeared. The loss of weight



Fig 1—Roentgenologic appearance of the stomach on July 24, 1928. The prepyloric deformity was constant fluoroscopically and in a series of films.

during the two months preceding admission was estimated as 10 pounds (4.5 Kg). The accompanying weakness was profound.

Physically, the patient was fairly well nourished and did not appear anemic. Abdominal examination disclosed, in addition to the previous operative scar, a midepigastriac mass which was freely movable and devoid of tenderness. No other noteworthy abnormalities were recorded. Aspiration after an Ewald test meal yielded 120 cc of gastric contents with 18 per cent free and 30 per cent combined acidity. The chemical test for occult blood was positive both for the contents of the stomach and for those of the stools. Roentgen examination of the stomach

with barium sulphate (fig 2) demonstrated a constant annular deformity of irregular density and contour involving the pars pylorica and the distal portion of the pars media. This lesion occasioned retention of 50 per cent of the six hour meal. The roentgen diagnosis was carcinoma. The Wassermann reaction was negative.

The patient was transferred to the surgical service with a preoperative diagnosis of gastric carcinoma superimposed on a peptic ulcer. Laparotomy, performed on April 4, 1930, disclosed a semielastic tumor involving the distal third of the



Fig 2—Roentgenogram of the stomach taken on March 27, 1930, demonstrating the annular constricting deformity involving the pars pylorica and the distal portion of the pars media.

stomach, with a number of enlarged perigastric glands as large as hazelnuts. The surgeon decided to delay radical resection until the general condition of the patient could be improved through relief of the obstruction. He therefore performed a posterior gastro-enterostomy. Convalescence was uneventful until the morning of April 23, nineteen days after operation, when the patient complained of epigastric pain. Shortly before midnight emesis occurred and this was repeated several times on the following day. Acute gastric dilatation was suspected, and lavage

was instituted. On the morning of April 25, the patient complained of abdominal pain, but he was not believed to be in a serious condition. In the afternoon, following copious emesis of a greenish fluid, the patient rapidly weakened and died.

Autopsy—The postmortem examination was made by Dr. R. H. Jaffe, who pointed out the following pertinent conditions. Although the abdomen was somewhat scaphoid, the stomach, duodenum and proximal jejunum were enormously dilated. The lack of abdominal distention was due to the fact that the gastric dilatation involved merely the proximal two-thirds, which buried itself subcostally and forced the diaphragm upward. The distal one-third of the stomach lacked distensibility on account of the presence of a rigid infiltrating tumor. Eleven centimeters from the duodenojejunal junction, the intestine was twisted at an angle of 90 degrees, and it was surgically anastomosed to the stomach. Through the loop formed by that portion of jejunum that was fixed by the ligament of Treitz on the one hand and the point of anastomosis on the other, herniation of the remainder of the jejunum and all but the terminal ileum had occurred. The herniated loops were readily reduced, and normal conditions were thereby restored. Death was assigned directly to the high-lying obstruction caused by the internal incarceration.

Except with regard to the stomach and perigastric lymph glands to be described in detail, the postmortem observations require no elaboration for purposes of this paper. A painstaking search disclosed no gross evidence of lymphogranulomatosis other than in the stomach, the beginning duodenum and the perigastric lymph glands. The essential changes noted at necropsy are epitomized in Dr. Jaffe's anatomic diagnosis, which was: Hodgkin's lymphogranuloma of the distal portion of the stomach, the beginning duodenum and the perigastric lymph glands, recent gastrojejunostomy, herniation and incarceration of the small intestines through the anastomotic loop, high intestinal obstruction, recent fibrinous peritonitis, chronic focal bronchopneumonia of the left lower pulmonary lobe, inflammatory softening of the spleen, cloudy swelling of the liver, the kidneys and the myocardium, generalized emaciation, brown atrophy of the myocardium, endocardial sclerosis, and fibrous obliteration of both of the pleural cavities.

Gross Description of the Lymphogranulomatous Lesions—The stomach was greatly enlarged, owing to a marked dilatation of the proximal two-thirds. The distal one-third, which was free from distention, was the seat of a soft, somewhat elastic infiltration which began 7.5 and 23 cm. proximal to the pyloric ring on the lesser and greater curvatures, respectively, and terminated 22 cm. distal to the pyloroduodenal junction. There was no gross extension of the tumor beyond the gastric or duodenal walls.

On opening the stomach (fig. 3), the dilated portion was seen to be finely mammillated, devoid of rugous folds and intact. The wall was thinned in proportion to the degree of distention of the organ. A recent, functioning gastro-enterostomy stoma was present on the posterior wall proximal to the infiltration. A tumor occupied the distal one-third of the stomach, and had produced a marked thickening of the gastric wall without leading to stenosis of the lumen. The circumference of the pyloric ring, as measured on the inside of the stomach, was 4 cm. The gastric circumference was 7.5 cm. at a point 2 cm. proximal to the ring. The lining of the infiltrated portion of the stomach was grayish white and extensively ulcerated. The ulcerations were for the most part superficial and irregular in outline, and they possessed sloping edges. Nowhere did the base of an ulcer extend below the level of the normal mucosa. The borders of the infiltrate were slightly raised and could be clearly defined, the proximal one being roughly scalloped and the distal one only slightly wavy in outline.

The cross-section of the wall of the stomach in the involved area (fig 4) exhibited a striking increase in thickness, which reached its maximum at a point 5 cm proximal to the pylorus where it measured 2.5 cm. In passing both caudad and cranial from the point of maximum thickness, there was a gradual tapering down until the limits of the tumor were reached. The increase in thickness was due to grayish-white, homogeneous, adenoid-like tissue, succulent and semifirm in consistency. The identification of the individual layers was obscured except at



Fig 3—The interior part of the stomach. The greater portion of the anterior wall has been removed. The gastro-enterostomy stoma is situated proximal to the upper margin of the granulomatous infiltrate.

the extremities of the growth where the gray muscularis could be seen subjacent to the white foreign tissue.

A number of the lymph glands in the gastrohepatic omentum, located in the prepyloric area, were increased in size, the largest measuring 3 cm in diameter. The tissue comprising these glands was identical with that noted in the stomach. A few prepyloric glands similar to but smaller than those in the lesser omentum were found in the gastrocolic ligament. The peripancreatic and periaortic glands were not enlarged.

Microscopic Description—Sections from various portions of the stomach and from the pyloroduodenal junction showed essentially the same changes and therefore lend themselves to a composite description. Figures 5 and 6 furnish representative pictures of the histopathologic condition found. Since the morphologic details differed in no way from the microscopic appearance of Hodgkin's disease found elsewhere, the finer minutiae can be omitted.

The mucosal layer was almost completely replaced by a granulation tissue consisting of short, spindle-shaped fibroblasts and thin-walled capillaries, in which the following types of cells were embedded: round cells of a lymphocytic character, mainly small, larger cells with barely discernible cytoplasm containing large, oval and round, pale, vesicular nuclei, eosinophils and plasma cells of the usual type, distinctive giant cells with large, round, irregular or lobulated nuclei that were rich in chromatin with distinctly oxyphilous nucleoli. At times these giant cells

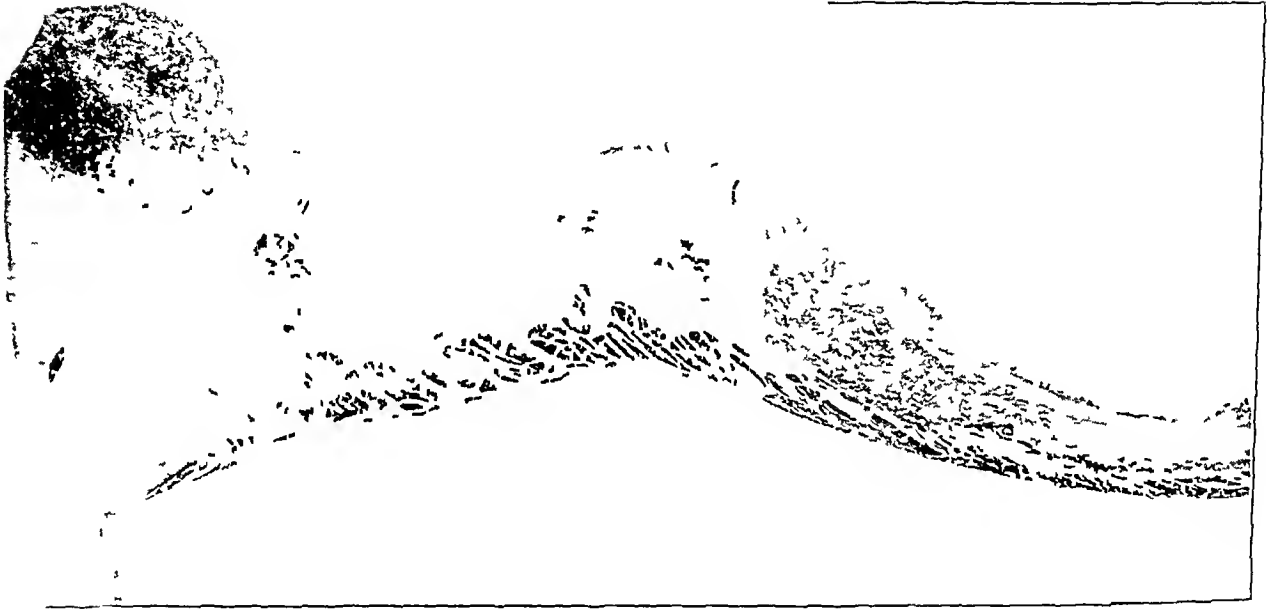


Fig 4—Cross-section of the gastric wall taken from the region proximal to the area of maximum thickness

(Sternberg-Reed) appeared multinucleated. The round cells and histiocytes predominated. Eosinophils were prominent, whereas plasma cells were encountered relatively infrequently. The Sternberg-Reed giant cells were numerous, as many as 15 being found in a single, high power field. Only a few widely separated, but well preserved, glandular elements remained to indicate the site of the original tunica propria. The muscularis mucosa was almost completely destroyed.

The prodigious thickening of the involved area was due mainly to the increase of the submucous layer, which in places constituted as much as nine tenths of the gastric wall. Throughout the involved portion the infiltration in the submucosa passed imperceptibly into the overlying mucosa. Where the involvement was minimal, the cellular accumulations of the submucosa were separated from the muscularis by a condensation of collagen fibers only slightly infiltrated by cellular elements. In approaching the areas of maximum involvement, this fibrous septum became more and more obscured by extensions of dense cellular infiltrates which obliterated the zone of division between the submucous and muscular layers. In

a number of areas, the polymorphocellular character of the infiltrate was striking whereas in other areas consisting mainly of histiocytes the appearance was relatively uniform. The invading and proliferated cells comprising the submucosa were identical with those found in the mucosa.

The muscular layer appeared fairly normal in the areas of least involvement. As the region of maximum infiltration of the gastric wall was approached, extensions from a fibrous layer in the floor of the submucosa insinuated themselves between the bundles of muscle. Progressing still further, one found numerous cells embedded in, and augmenting, the invading fibrous septums. The muscular

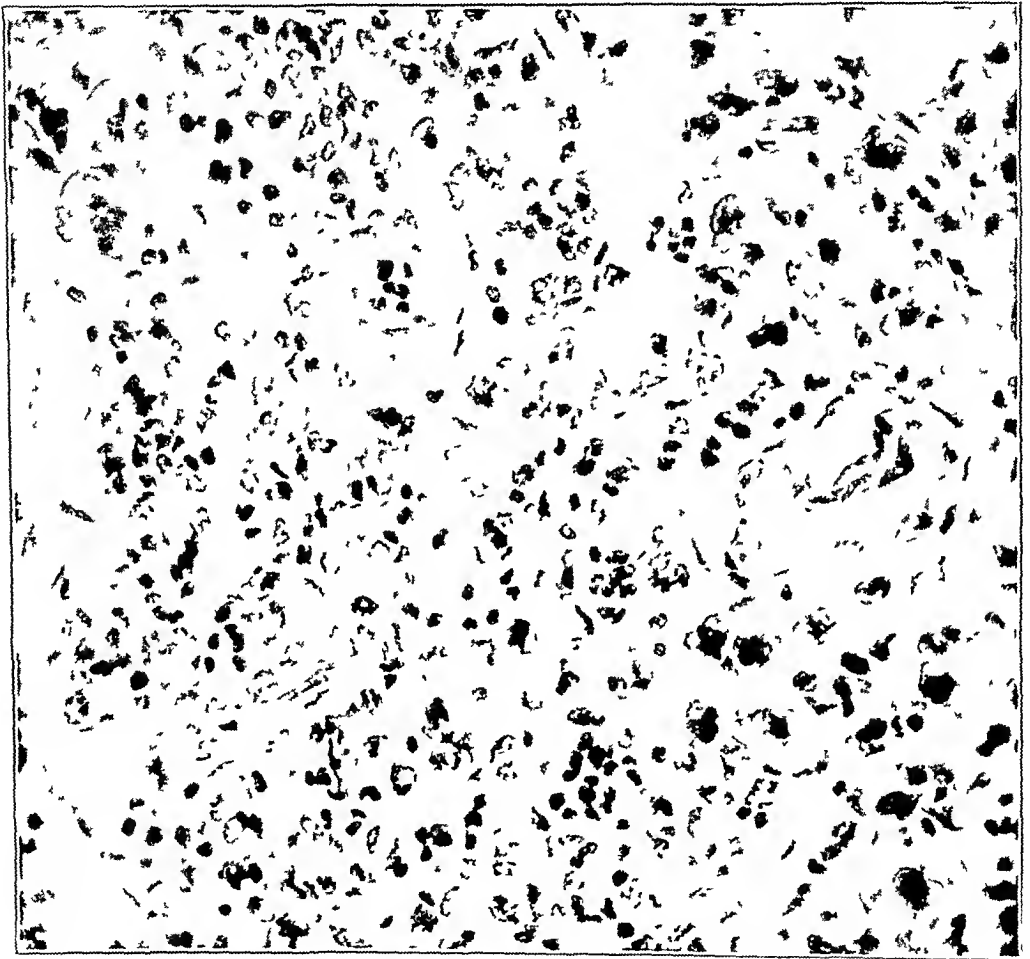


Fig 5—Photomicrograph of the mucosa, illustrating the polymorphocellular character of the granuloma, $\times 400$

layer still retaining its identity, was notably increased in thickness as a result of this fibrocellular incursion. Gradually the cellular elements became more and more numerous and the elements of the muscle and the connective tissue less and less conspicuous, until they were completely obscured. The individual cells comprising the infiltrates did not differ from those present in the overlying layers.

A slight increase of the serous coat due mainly to fibroblasts and edema fluid was noted in the portions with minimal thickening. Passing toward the area of greatest involvement one found that the layer became invaded by an increasing number of cellular elements until the point was reached where the thickened

serosa coalesced with the muscularis. Here, identification of individual layers was impossible, and the entire gastric wall assumed a uniform appearance. The infiltrated cells of the serosa were mainly of the round type, associated principally with plasma cells and histiocytes. Sternberg-Reed giant cells were infrequent in this layer.

The histologic appearance of the lymph nodes located in the region of the tumor was practically identical with that of the gastric wall in the region of

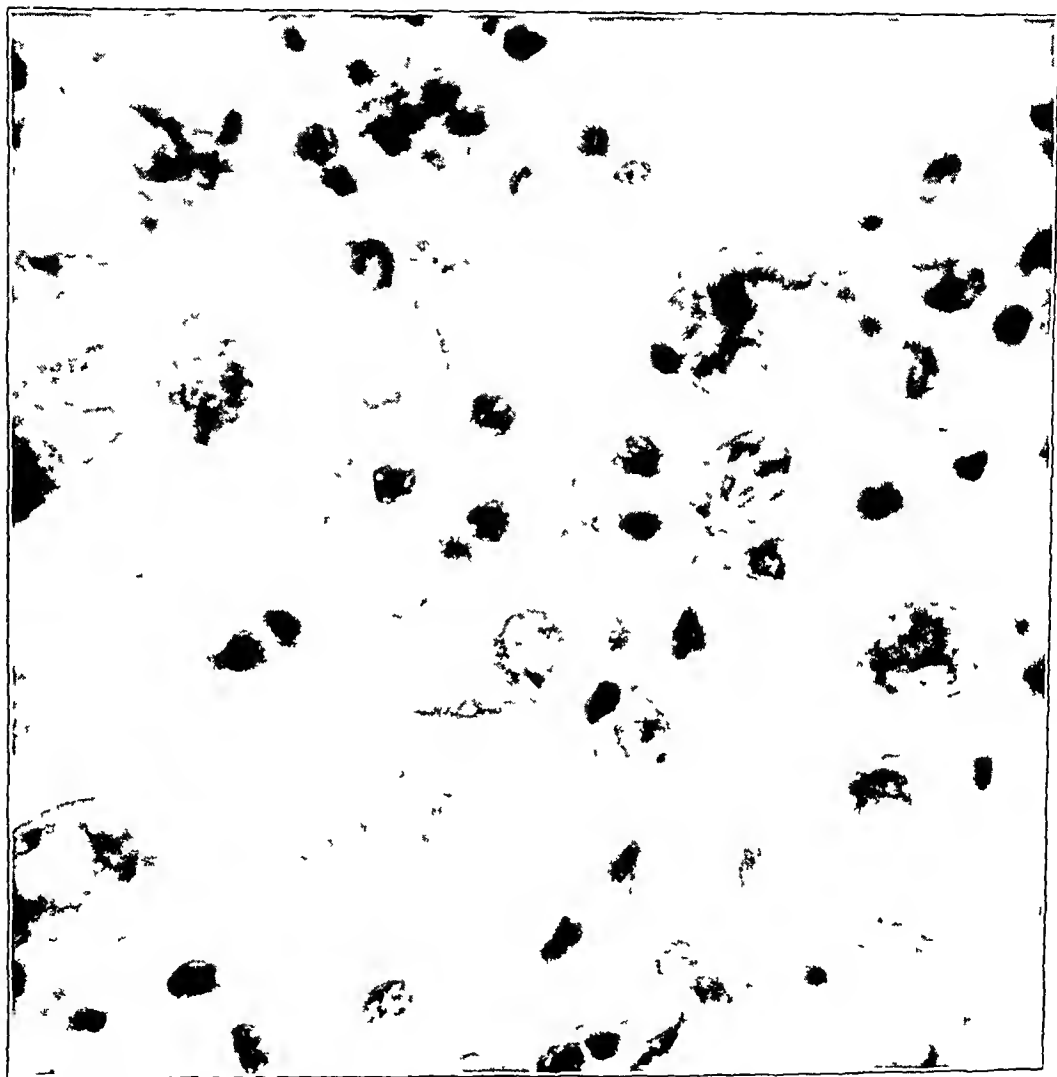


Fig 6—A field from the mucosa exhibiting the pleomorphism and finer morphologic structure of the Sternberg-Reed giant cells, $\times 1,100$

maximum involvement. The characteristic polymorphocellular granulomatous tissue, with an abundance of monolobulated and multilobulated giant cells, was well exhibited. Changes suggestive of Hodgkin's disease were not noted in other sections.

COMMENT

That Hodgkin's disease may begin primarily, not only in lymph glands, but also in the adenoid structures of various organs is firmly

established. Acknowledging a primary origin in the gastro-intestinal tract, it would seem, theoretically, that surgical extirpation would be the treatment of choice in localized cases. The fact that lymphogranulomatosis, although probably inflammatory, behaves clinically like a malignant growth does not militate against the justification of the desirability of radical removal. As Pissarewa contended, no one would refrain from operation in the case of an operable carcinoma merely on account of a possible recurrence and unfavorable outcome. Nor would one allow a localized tuberculous focus to remain untouched in the gastro-intestinal tract because it is inflammatory. In the absence of any other known effective and reliable therapeutic agent, the inherent character of the disease, the tendency to recurrence and the fatal outcome do not constitute valid objections to surgical removal. Particularly is this true with regard to isolated lesions of the stomach when early recognition is feasible, the involved organ is accessible and the operative danger is relatively slight. Naturally, discretion must be exercised in selecting the cases for operation since a radical operation in a patient with less disseminated lymphogranulomatosis is as futile as in a patient with diffuse carcinomatosis or sarcomatosis. It is, of course, necessary to keep in mind that the presence of small lesions outside of the digestive tract that do not permit clinical demonstration or identification cannot be eliminated and that, therefore, a guarded prognosis should be made in all cases.

These theoretical considerations receive support from practical experiences with isolated lymphogranulomatosis of the gastro-intestinal tract. With regard to the stomach, the cases of Steindl¹⁰ Fioboese¹⁰ and Vasiliu¹¹ are particularly noteworthy. Steindl's patient was free from evidence of recurrence when last observed a year after resection. Until the time of publication of Fioboese's report, which was five months after operation the patient had not returned for medical aid and she was assumed to be in good health. The most striking surgical result was obtained in the case of the medical student reported by Vasiliu. The patient following a gastric resection in 1926, completed her medical course and was entirely well when last observed, in 1929. It is likely that within the series of the resected cases of lymphoblastoma with favorable outcome reported by Holmes, Dresser and Camp¹¹ one or more instances of Hodgkin's disease are included. Should recurrences or independent foci subsequently appear their presence will hardly detract from the value of the treatment which has been instituted. A few years of relief from symptoms justifies a radical procedure as illustrated in the following case of intestinal

¹⁰ Holmes G W Dresser R and Camp J D Lymphoblastoma Its Gastric Manifestations with Special Reference to the Roentgen Findings Radiology 7 44 (July) 1926

lymphogranulomatosis Biebl²⁰ recorded that a man, aged 25, who complained of symptoms referable to the lower part of the abdomen, underwent resection of the small intestine and the attached portion of the urinary bladder on June 12, 1920. The microscopic diagnosis was lymphogranulomatosis. The patient remained well for five years when symptoms referable to the upper part of the abdomen appeared. These had been present six months when, on Dec. 31, 1925, the patient was operated on for a perforative peritonitis and 40 cm. of lymphogranulomatous jejunum was resected. White nodes and infiltrates were in the omentum and the mesentery. The patient again made an uneventful recovery and returned to his occupation as a farmer.

Since available evidence indicates that surgical measures are of value in the treatment for isolated gastric lymphogranulomatosis, it follows that the diagnostic aspects of the disease merit consideration. In no case of primary, isolated, gastric Hodgkin's disease has the diagnosis been made prior to the operation or autopsy. This statement is not surprising in view of the fact that clinically there is no local feature of the disease that, in the present state of knowledge, is distinctive. Carcinoma of ulcer is generally diagnosed, particularly the former. Characteristic systemic manifestations are, as a rule, lacking in the localized stage. Paroxysms of fever (Pel-Epstein), which are highly suggestive of Hodgkin's disease, are generally absent until the disease becomes more or less disseminated. Sussig's¹⁵ patient, in whom the disease was not actually isolated, but rather localized to the region of the stomach, suffered from an intermittent type of high temperature which reached 41 C (105.8 F). In all three cases of lymphogranulomatosis with gastro-intestinal involvement observed by Sussig, he noted the association of an intermittent fever, a brownish-red discoloration of the skin and excessive desquamation of the epidermis involving especially the soles and the palms. Other authors have not observed this syndrome, and therefore no diagnostic importance can be attached to it. The hematologic features of eosinophilia and monocytosis are, like fever, usually absent in cases with isolated lesions. In the case of Bianchi¹⁷ in which the diagnosis of Hodgkin's disease was made on hematologic and clinical evidence, the gastric lesion formed only part of a generalized involvement.

Although isolated gastric lymphogranulomatosis cannot be diagnosed by current clinical methods the lesion usually leads to surgical exploration when its presence can at least be suspected. Steindl⁵ noted in his case that the pyloric tumor was flat infiltrating soft and resilient and was accompanied by many isolated glands as large as a hazelnut. From the gross characteristics of the gastric tumor and the adjacent nodes

²⁰ Biebl, M. Beitrag zur intestinalen Lymphogranulomatose. Deutsche Ztschr. f. Chir. **198** 104 (Aug.) 1926.

he suspected the presence of a lymphosarcoma or tuberculosis. In Kaznelson's²¹ description of operative observations, he mentioned a circular infiltration of the pylorus which gave the impression of a benign stenosis rather than of a malignant condition. The mesenteric lymph glands were recorded to be from the size of a hazelnut to that of a walnut. In the case here reported the gastric infiltration resembled that found in syphilis of the stomach, but the number and character of the glands were not in accord with a diagnosis of gastric syphilis. From a consideration of the facts available, the disclosure at operation of a soft, flat, infiltrating tumor limited to the distal portion of the stomach, associated with many isolated, relatively large, soft, cream-colored, succulent glands, should arouse the suspicion of a gastric lymphogranulomatosis. There is another type of lymphogranulomatous infiltration in which the gastric folds bear a close resemblance to cerebral convolutions as described by Sternberg¹⁸. This form tends to involve the stomach diffusely and can readily be confounded with gastric aleukemic lymphadenosis.

For a final diagnosis the use of the microscope is indispensable. Even after histologic sections are available, the interpretation is not always a simple matter especially in the early stages, as exemplified in the initial biopsy of the generalized case reported by Hayden and Apfelbach¹⁴. The main difficulty lies in distinguishing between lymphosarcoma and lymphogranulomatosis. In the case of Hodgkin's disease reported by Terplan and Wallesch²² the microscopic changes in blocks from certain parts of the gastro-intestinal tract did not permit differentiation from a lymphoblastic sarcoma. Differentiation between lymphosarcoma and Hodgkin's disease could not be made from the histologic appearance of the primary tumor in the case described by Pamperl and Terplan²³. In the adjacent mesenteric lymph glands, however, the morphologic appearance was characteristic of lymphogranulomatosis. Another possibility of error in bioptic diagnosis, which is remote, however, was mentioned by Konjetzny¹⁷. This author recorded a case of colloid carcinoma of the pylorus with carcinomatous glands in the adjacent area and lymphatic nodes as large as walnuts extending along the lesser curvature and reaching to the cardia. The latter glands which at the operation were assumed to be carcinomatous, proved microscopically to be lymphogranulomatous.

21 Kaznelson P. Ueber einen Fall von Nischenbildung und Pylorusstenose infolge Lymphogranulomatose des Magens, *Wien Arch. inn. Med.* **7** 117 1923.

22 Terplan K. and Wallesch E. Ein Fall von intestinaler Lymphogranulomatose *Med. Klin.* **19** 1428 (Oct. 28) 1923.

23 Pamperl R. and Terplan C. Ein Beitrag zur intestinalen Lymphogranulomatose *Med. Klin.* **21** 1679 (Nov. 6) 1925.

The effect of irradiation on lymphogranulomatous tissue, especially in the hyperplastic stage, renders the roentgen rays of some diagnostic, as well as therapeutic, value. When surgical intervention is contra-indicated, a response to roentgen treatment would place the case in the group of so-called malignant lymphomas. Holmes, Dresser and Camp¹⁹ recorded a case in a woman, aged 64, who had been receiving treatment with roentgen rays for enlarged peripheral lymph nodes, which were proved by biopsy to be lymphoblastomatous. The development of gastric symptoms led to an examination with a barium meal. An irregular filling defect devoid of peristalsis was found involving the lower third of the stomach. After roentgen irradiation the gastric symptoms improved, and the filling defect diminished in extent, it became difficult of demonstration and no longer interfered with the passage of peristaltic waves. Little need be said regarding the therapeutic value of the roentgen rays in inoperable gastric lymphogranulomatosis. If nothing more, at least a great deal of suffering can be spared the patient by the judicious use of the roentgen rays. In any case in which the possibility of a lymphogranulomatous process may be entertained, the surgeon should remove a gland for biopsy. If carcinoma is discovered nothing is lost. If, on the other hand, the tumor proves to be Hodgkin's disease, the patient's suffering may be ameliorated and his life prolonged by roentgen therapy.

SUMMARY

Pathologists have known for many years that lymphogranulomatosis may have its origin, not only in lymph glands, but in any organ or structure that normally contains adenoid tissue. The fact that primary growths were known to occur in the spleen, the liver, the bone-marrow and the lung attracted little surgical attention on account of the inherent difficulties that lay in the way of early diagnosis and of surgical extirpation. With regard to primary diseases of the gastro-intestinal tract and particularly of the stomach, prompt manifestations are the rule, diagnosis of the presence of a lesion is not difficult, and surgical removal is relatively safe.

Six cases of primary isolated Hodgkin's disease of the stomach are recorded in the literature. The preoperative diagnosis was either carcinoma or ulcer and gastric resection was performed in all of them. Five patients recovered and remained well for as long as they were observed. A sixth patient died, a month after operation, from obstruction at the stoma. No gross evidence of other lymphogranulomatous lesions was found post mortem, but no mention of microscopic examination of the various organs was made. The seventh case of isolated Hodgkin's disease of the stomach, the first to be reported in this country, is unique in that a complete history and a painstaking gross

and microscopic examination at necropsy failed to disclose any previous or associated lesion elsewhere in the body.²⁴

The clinical diagnosis of isolated lymphogranulomatosis of the stomach is hardly possible in the present state of knowledge. The systemic and hematologic manifestations are generally absent when the lesion is still in the operable stage. At operation the presence of a soft flat infiltrating tumor strictly limited to the distal portion of the stomach associated with a disproportionate number of large, succulent isolated adenoid-like glands should suggest the possibility of a lymphogranulomatosis. The final diagnosis is a histologic one. In any case of inoperable tumor of the stomach in which the possibility of Hodgkin's disease is to be considered biopsy should not be omitted.

Even when a careful exploration fails to demonstrate evidence of granulomatous tissue other than that extirpated, a guarded prognosis should be made. Gross lesions in inaccessible regions and microscopic involvement of the structures examined at the operating table may coexist without the possibility of detection. When the extent of involvement precludes resection the patient should be given the benefit of roentgen therapy.

24 Since the completion of this manuscript my attention was directed to an article by Dr V. C. David (Pseudocarcinoma of the Stomach, *Ann Surg* 87:555 [April] 1928) in which he describes a woman, aged 50, who had suffered from abdominal complaints for three months and who presented roentgen evidence of a filling defect of the antrum. A preoperative diagnosis of carcinoma of the stomach was made. The gastric tumor which was resected by Dr. Dean Lewis proved microscopically to be lymphogranulomatous. The report stated that subsequently enlarged glands developed, which receded under roentgen treatment, following which a rectal mass, presumably a Hodgkin's infiltration, appeared. A personal communication from Dr. Dean Lewis indicates that no lesion other than the one in the stomach was demonstrable at the time laparotomy was performed and that for over two years no other evidence of Hodgkin's disease could be detected.

THE ETIOLOGY AND PATHOLOGY OF CYSTS OF THE PANCREAS

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In a previous communication¹ we reported on a clinical study of forty-seven cases of pancreatic cysts treated surgically at the Mayo Clinic in the last ten years. In this paper we shall consider (1) the pathogenesis of cysts of the pancreas, (2) our classification and (3) the pathologic manifestations of such cysts. As a basis for our study, we reviewed the literature, the records at the clinic and the operative and necropsy material obtained in eighty-eight cases of cysts of the pancreas treated surgically, as well as that in twenty cases in which such cysts were discovered incidentally at necropsy.

Comparatively little experimental work has been done on the production of cysts in the pancreas. Senn² ligated the pancreatic duct in dogs but was unable to produce a cyst, although it appeared that ectasia of the duct followed the ligation. He concluded that factors other than mere obstruction were instrumental in the production of cysts. He suggested that the secretion failed to absorb. Thuroloix³ ligated the accessory pancreatic duct in the dog and injected 7 cc of a mixture of soot and phenolized liquid petroleum into the duct of Wirsung. The vertical part of the gland was removed. A large cyst was found in the splenic portion of the gland when the animal was killed almost three months later. This cyst contained clear fluid and hard irregular calculi of about 1 mm in diameter. Lazarus⁴ crushed the pancreas of a dog and produced a hematoma. Six weeks later a cyst "the size of a goose egg," which contained a milky fluid, was found. Binet and Brocq⁵ injected

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• 1 Judd, E S, Mattson, Hamlin, and Mahorner, Howard R. Pancreatic Cysts. Report of Forty-Seven Cases, *Arch Surg* **22** 838 (May) 1931

2 Senn, Nicholas. The Surgery of the Pancreas as Based upon Experiments and Clinical Researches, *Am J M Sc* **92** 141 (Jul) 1886, **93** 121 1887, *Experimental Surgery*, Chicago, W T Keener, 1889

3 Thuroloix, J, quoted by Oser. Diseases of the Pancreas in Nothnagel Encyclopedia, Philadelphia, W B Saunders Company 1903

4 Lazarus Paul. Beitrag zur Pathologie und Therapie der Pankreaserkrankungen mit besonderer Berücksichtigung der Cysten und Steine, *Ztschr f klin Med* **51** 95 and 203 1904, **52** 146 and 381, 1904

5 Binet, Leon, and Brocq Pierre. Reproduction expérimentale de la pancréatite hémorragique avec steato-nécrose et du pseudo-kyste pancréatique par l'injection de sels de calcium dans le canal de Wirsung. *Compt rend Soc de biol* **83** 341 (March) 1920

a solution of calcium chloride into the duct of Wirsung of a dog and produced acute hemorrhagic pancreatitis, and in one instance a pseudocyst. They concluded that the reaction resulted from the activation of the trypsinogen by the calcium chloride, since it did not follow the injection of a solution of sodium fluoride. Opie⁶ called attention to the relationship between diseases of the pancreas and the obstruction of the normal outflow of bile by a stone in the common bile duct. Archibald⁷ found that bile injected into the pancreatic duct produced pancreatitis; if the bile was infected the results were more marked.

It may be said that most of the experimental evidence concerning the production of cyst of the pancreas is inconclusive. Yet the results, when correlated with clinical observations in man, throw light on the manner in which certain of these cysts are formed.

After a study of the different types of cysts of the pancreas we made a classification which is based on their etiology.

- I Cysts resulting from defective development
 - (1) Cysts in infants
 - (2) Cysts associated with polycystic disease of the kidney
 - (3) Dermoid cysts
 - (4) Inclusion cysts
- II Cysts resulting from trauma
- III Retention cysts
- IV Neoplastic cysts
 - (1) Cystadenoma
 - (2) Cystadenocarcinoma
 - (3) Teratomatous cysts
- V Cysts resulting from parasites

CYSTS RESULTING FROM DEFECTIVE DEVELOPMENT

Cysts in Infants—Fault of development of an acinus or a duct in some instances apparently plays a part in the formation of cysts of the pancreas. Such cysts are found rarely in infants. Connolly⁸ reported a case in a child aged 14 months. Railton⁹ reported a case of pancreatic cyst in a child aged 6 months, and Eha¹⁰ reported a case in an infant.

6 Opie, E. L. The Relation of Cholelithiasis to Disease of the Pancreas and to Fat Necrosis, *Am J M Sc* **121** 27 (Jan.) 1901, Diseases of the Pancreas, Philadelphia, J. B. Lippincott Company, 1910.

7 Archibald, E. The Experimental Production of Pancreatitis in Animals as the Result of the Resistance of the Common Duct Sphincter, *Surg Gynec Obst* **28** 529 (June) 1919.

8 Connolly, D. I. Note on a Case of Pancreatic Cyst in a Child Aged 14 Months. *Lancet* **1** 803, 1911.

9 Railton, T. C. A Case of Pancreatic Cyst in an Infant. *Brit M J* **2** 1318, 1896.

10 Eha, C. E. Case of Congenital Pancreatic Cyst, *J A M A* **78** 1294 (April 29) 1922.

aged 5 months. He thought that the cyst was congenital. The part that trauma at birth may have played cannot be overlooked.

Cysts of the Pancreas Associated with Polycystic Disease of the Kidney—Cysts of the pancreas, like those of the liver, are sometimes associated with polycystic disease of the kidneys. In one of our necropsy cases, bilateral polycystic kidneys, multiple cysts in the liver and a few cysts in the head and the adjacent part of the body of the pancreas, of from 1 to 2 mm in diameter, were found. These cysts were thin-walled and contained clear fluid. They were lined with a single layer of cuboidal epithelium. Kaufmann¹¹ also observed cysts in the pancreas associated with polycystic disease of the kidneys. Judd¹² found a congenital cystic kidney at an operation that was performed for cyst of the pancreas.

Dermoid Cysts—In the pancreas, dermoid cysts are rare. One was removed successfully by Judd; the case was reported in detail by Masson and Caylor.¹³ Another case was reported by Dennis.¹⁴ These cysts contain hair and caseous material, and microscopically the walls show the picture characteristic of dermoid cysts (fig. 1).

Inclusion Cysts—These cysts have developed in an organ from cells which are not normally there, but which were incorporated in the organ from some extraneous tissue by a fault of development in embryonal life. The remote possibility that such cysts may be present in the pancreas should not be overlooked. Carling and Hicks¹⁵ expressed the belief that certain true cysts of the pancreas are the result of inclusions of portions of the wolffian body.

CYSTS RESULTING FROM TRAUMA

Injury to the abdomen precedes the development of cysts of the pancreas with significant frequency in the various series of cases reported in the literature. Some patients give a definite history that the mass developed directly following injury. These facts, together with the experimental evidence produced by Lazarus, point to trauma as a factor in the development of certain cysts of the pancreas.

The term pseudocyst is found in the literature and is intended to include extraparenchymal or interparenchymal cysts, which are not and

11 Kaufmann, Eduard. *Lehrbuch der speziellen pathologischen Anatomie*, Berlin, Walter de Gruyter & Company, 1922, Pathology for Students and Practitioners. Philadelphia, P. Blakiston's Son & Company, 1929.

12 Judd, E. S. Cysts of the Pancreas, *Minnesota Med.* 4: 75 (Feb.) 1921.

13 Masson, J. C., and Caylor, H. D. Dermoid Cyst of the Pancreas, *Surg. Clin. North America* 9: 837 (Aug.) 1929.

14 Dennis, W. A. Dermoid Cyst of the Pancreas, *Surg. Clin. North America* 3: 1319 (Oct.) 1923.

15 Carling, E. R., and Hicks, J. A. A Consideration of Two Cases of Cystadenoma of the Pancreas and Their Probable Relationship to Polycystic Conditions Found in Other Viscera. *Brit. J. Surg.* 13: 238 (Oct.) 1925.

which were not at any time in their development lined with epithelium. Practically it is impossible to distinguish true cysts and pseudocysts, because true cysts sometimes lose their epithelial lining, they are then in no way different morphologically, from cysts that are traumatic in origin.

Lloyd¹⁶ reported two cases of cyst of the pancreas with the observations at operation and called attention to the fact that many of the so-called hemorrhagic cysts of the pancreas are in reality hemorrhages into the lesser peritoneal cavity. The two cysts that he reported were undoubtedly of traumatic origin, and yet he recovered trypsinogen from



Fig 1—Wall of a dermoid cyst of the pancreas (case reported by Masson and Caylor)

the fluid that drained from them. Warnock¹⁷ reported the case of a boy, aged 7 years, in whom a mass developed in the upper part of the abdomen after severe trauma. At operation a pancreatic cyst was found. Such cases leave little doubt that trauma causes cysts. Of the one hundred and nineteen cases reviewed by Korte,¹⁸ there was a definite history of injury in thirty-three (28.2 per cent). In Judd's series there was a

16 Lloyd, Jordon. Injury to the Pancreas. A Cause of Effusions into the Lesser Peritoneal Cavity, *Brit M J* 2 1051 1892.

17 Warnock, H. A. Pseudocyst of the Pancreas, *Brit M J* 1 104 (Jan 19) 1929.

18 Korte, Werner. Die chirurgischen Krankheiten und die Verletzungen des Pankreas, Stuttgart, Ferdinand Enke, 1898.

history of trauma in 24 per cent, and in McWhorter's¹⁹ series 15.7 per cent of the patients gave a history of abdominal injury.

In the forty-seven cases of cyst of the pancreas in which surgical procedures had been carried out at the Mayo Clinic since Judd's report in 1921, there was a history of trauma preceding the onset of symptoms in eight (17 per cent).

A man, aged 27, was struck in the abdomen in an automobile accident a month before the onset of pain and swelling in the left part of the abdomen. Eight hundred cubic centimeters of straw-colored fluid was drained from a benign cyst five months after the accident. The discharge continued for three months, then the wound closed, and the patient recovered uneventfully.

In a case of fracture of a cervical vertebra from a fall, the patient, a man aged 65, began to feel fulness in the left upper part of the abdomen six years later, this continued for twenty years. Operation was performed, and a malignant pancreatic cyst was found.

A woman, aged 63, had fractured two ribs in a fall six months before the beginning of symptoms. One year after the accident a laparotomy was performed, and a pancreatic cyst was found. The pancreas was hard and nodular, and a malignant lesion was suspected. The patient died elsewhere six months after the operation. We did not obtain further information.

A farmer, aged 30, was struck in the right side of the abdomen by a steering wheel. Three days later he noticed abdominal swelling. Operation was performed seven months after the accident, and a pancreatic cyst containing 1 liter of clear fluid was drained.

A woman, aged 40, suffered a blow in the upper part of the abdomen in a railroad wreck. Examination at the clinic, almost a year after the accident, disclosed an epigastric mass. On exploration, the mass proved to be a pancreatic cyst which contained about 1 liter of hemorrhagic fluid.

A patient, aged 41, was struck in the abdomen in an automobile accident. An emergency operation was performed at once elsewhere, and about 4 liters of clotted blood was removed from the abdomen. Yellowish fluid discharged intermittently from a sinus. Three months after the accident the abdomen was explored, and about 1 liter of cloudy fluid was drained from a cyst which apparently was attached to the pancreas.

In another case, a man, aged 41, tripped and fell while he was running, he remained unconscious for five minutes. He bled profusely from the nose, and vomited. The abdomen was painful and rigid. The upper part of the abdomen became enlarged and remained so. About 6 liters of bloody fluid was drained from a pancreatic cyst thirty-eight days after the accident.

A patient aged 25 was in an automobile which turned over three times. The sixth, seventh and eighth ribs on the left side were fractured, and the patient was unconscious for six hours. Six days later he noticed a mass in the left upper part of the abdomen. At operation, a cyst of the pancreas was found.

In many cases of cyst of the pancreas following trauma, symptoms do not develop for weeks or months, although sometimes they appear at once. It is difficult to interpret the significance of such a long latent period. It is possible that cysts grow by the mere accretion of fluid due

19 McWhorter G. L. Cysts of the Pancreas. *Arch Surg* 11: 619 (Oct) 1925.

to a difference in the osmotic pressure. Perhaps after injury to the pancreas and the first hemorrhage the ferments erode the tissue, causing further hemorrhage and thus enlargement of the cyst.

The history in some cases suggested that trauma may be more indirect and still produce cysts. McCann,²⁰ Carslaw,²¹ Mayo²² and Russ²³ reported cysts of the pancreas that were observed during pregnancy or shortly after parturition. In three of eighty-eight cases in which the operation was performed at the clinic, the cyst of the pancreas was discovered during pregnancy or shortly after parturition. In two cases the gallbladder contained stones. The rupture of a vessel during the strain of parturition suggests itself as one possible method by which a cyst may develop. Russ supposed that in the case which he reported a hemorrhagic lesion occurring during the course of puerperal sepsis was the cause of the cyst. This brings up the possibility of the production of a cyst of the pancreas by an embolism, which, either sterile or infected, might produce necrotic areas subject to the action of the escaped pancreatic ferments with consequent sepsis, hemorrhage and the formation of a cyst.

RETENTION CYSTS

The part played by obstruction to the outflow of pancreatic secretion in the production of cysts is not well defined. Virchow,²⁴ in 1863, described uniform or irregular rosary-like dilatation of the pancreatic duct, which he termed pancreatic ranula. We have observed in a necropsy specimen an irregular dilatation of the duct distal to an area of stenosis produced by carcinoma in the head of the pancreas. Ligation of the pancreatic duct does not result in the formation of cysts, and there is little if any, dilatation distal to the point of ligation. Attention has been called to the fact that theoretically partial and not complete obstruction results in hydronephrosis and in dilatation of the biliary passages, and that this may likewise be applied to the pancreas. Virchow noted that pancreatic calculi are sometimes found in cysts of the pancreas, and he likened them to the calculi found in sublingual ranula. There were pancreatic calculi in only one of the cases in our series. It may be that gallstones lodged in the termination of the common bile duct obstruct the outflow of pancreatic fluid, thus acting as a factor in the production

20 McCann, F. J. A Large Pancreatic Cyst Simulating an Ovarian Tumor. *Proc. Roy. Soc. Med.* **4**: 235, 1912-1913.

21 Carslaw, R. B. Acute Pancreatitis Followed by Development of a Pancreatic Cyst, Recovery. *Lancet* **2**: 132 (July 16) 1921.

22 Mayo, W. J. Pancreatic Cyst, *Med. Rec.* **45**: 168 (Feb.) 1894.

23 Russ, W. B. Pseudocyst of Pancreas Apparently Due to Hemorrhagic Necrosis Occurring During the Course of a General Sepsis, *J. A. M. A.* **77**: 620 (Aug. 20) 1921.

24 Virchow, Rudolf. *Die krankhaften Geschwulste*, Berlin, August Hirschwald 1863, pp. 276-277.

of cysts Durante ²⁵ described a cyst which enclosed a softened pancreas, *Ascaris lumbricoides* occluded the pancreatic duct

More interesting than the mere passive rôle of obstruction is the possibility that gallstones in the end of the common bile duct may shunt bile into the pancreatic duct Binet and Brocq, Opie and Archibald have shown that acute hemorrhagic pancreatitis may be brought about by the influx of bile in the pancreatic ducts Perhaps the reaction in acute hemorrhagic pancreatitis and the injury of the tissues proceed to lysis, isolation of the fluid and the formation of a cyst Munzer ²⁶ considered the question of the formation of cysts by softening and even the softening occasioned in fat necrosis The softening resulting from an infarct, or the reaction to an infected embolus, may contribute in a similar manner to the production of a cyst Cysts that owe their origin to hemorrhage into the tissue (apoplectic cysts) and to softening are pseudocysts and are not lined with epithelium Lloyd and Israel ²⁷ observed a necrotic pancreas floating as a sequestrum in a cyst of the organ

Tilger ²⁸ advanced the theory that retention and obstruction to the outflow of secretion is brought about by the fibrosis following chronic interstitial pancreatitis He observed that the ducts and acini appeared to be snared off by proliferation of the interstitial connective tissue We have seen microscopic appearances suggesting such a method of formation (fig 2) We have found fields in which the interstitial connective tissue separated small, individual, microscopic cysts quite definitely Yet even in the same glands in which we have observed these appearances, there was only focal fibrosis Moreover, in a pancreas in which there is much interstitial fibrosis there may be no evidence of the formation of the cysts We have seen strikingly little fibrosis in glands containing simple cysts

NEOPLASTIC CYSTS

The term "proliferation cyst" is encountered frequently in the literature, and such cysts are included under neoplasms in our classification Neoplasms of the pancreas produce cysts in two ways by an inherent tendency in the growth to form a cyst lined with epithelium or by degeneration and liquefaction in the tumor Carcinoma of the pancreas, although relatively common, does not have a tendency to develop cysts However, in such a tumor we have observed microscopic cysts lined with epithelium

25 Durante, F Cisti da ritenzione del pancreas Arch ed atti d Soc ital di chir **9** 109, 1894, abstr Zentralbl f Chir **21** 424 (April) 1894

26 Munzer Max Pankreascysten, Centralbl f d Grenzgeb d Med u Chir **6** 490 573 and 664 1903

27 Israel, O Zwei Falle von Necrose innere Organe bei Diabetes Mellitus, Virchows Arch f path Anat **83** 181 (Jan) 1881

28 Tilger, Alired Beitrag zur pathologischen Anatomie und Aetiologie der Pancreas-Cysten Virchows Arch f path Anat **137** 348 (July) 1894

Cystadenoma—Ewing²⁹ stated that adenomas of the pancreas are somewhat rare and adenomas in which cysts form must, of course, be even more rare. The meager descriptive detail of the gross and microscopic appearances of some cysts reported in the literature as cystadenomas makes it difficult to accept many of them as true neoplasms. This fact has been emphasized by Fitz.³⁰ Multilocular cysts are not necessarily cystadenomas. Even in benign cysts there may be papillary ingrowths or cysts in the wall. Residual pancreatic tissue has been described in the walls of pancreatic cysts, and we have observed it also (fig. 3). There is a possibility that this tissue, isolated as it is from



Fig. 2—Interstitial tissue apparently snaring off acini and thus forming retention cysts

the pancreatic ducts, might give rise to retention cysts. Korte reviewed from the literature thirteen cases of proliferative cysts of the pancreas. In 1902, Fitz reviewed eight cases of cystadenoma and added one of his own. Malcolm³¹ described a cystic tumor of the pancreas that probably was a true neoplasm. There were many cysts in the tumor that were lined with epithelium. Kaufmann also reported a true cystadenoma of the pancreas.

29 Ewing, James. *Neoplastic Diseases*, Philadelphia: W. B. Saunders Company, 1929.

30 Fitz, R. H. Multilocular Cystoma of the Pancreas, *Am. J. M. Sc.* **120**: 184 (Aug.) 1900.

31 Malcolm, J. D. A Case of Complete Removal of a Multilocular Cystic Tumor of the Pancreas. *Lancet* **1**: 1676, 1906.

Only two cases of cystadenoma of the pancreas were found among the eighty-eight cases of cyst of the pancreas in which operation was performed at the Mayo Clinic and in the twenty cases noted at necropsy. In one of the cases a cyst had been drained in January, 1921. The pathologist reported cystadenoma. Between January, 1921, and March, 1923, the patient was operated on six times for cysts of the pancreas. The mass recurred in the form of multiple cysts containing a milky, or a thick, mucilaginous fluid. The patient died elsewhere on June 9, 1926, and we were unable to obtain any further information concerning the lesion. The second patient with benign cystic tumor of the pancreas came to necropsy. This patient died eleven days after an operation at

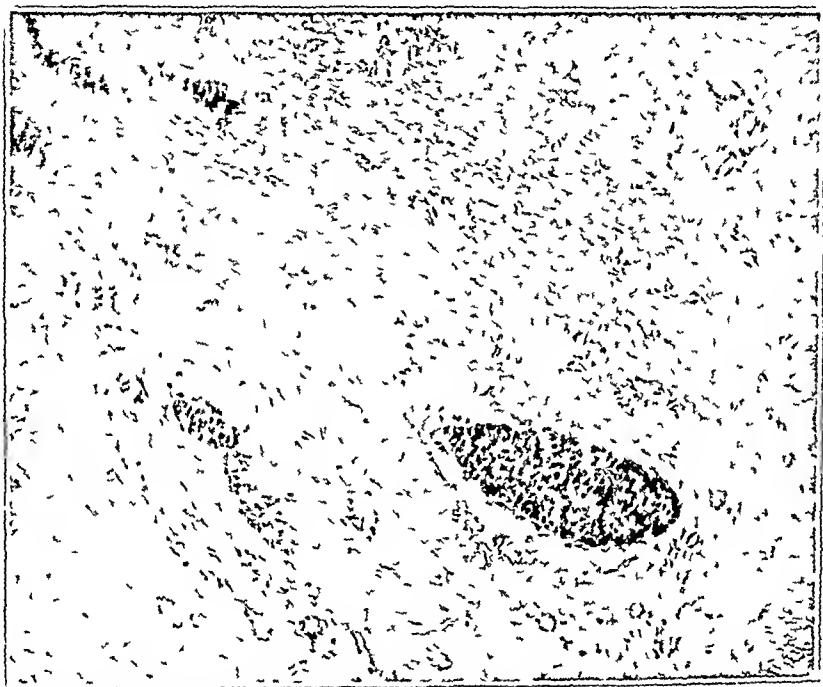


Fig 3—Residual pancreatic tissue in the fibrous wall of a simple multilocular cyst of the pancreas

which a large pancreatic cyst was drained. At necropsy it was found that the cystic tumor was fused to the head of the pancreas, it measured 12 by 12 by 7 cm, and the cavity, which made up about two thirds of the bulk of the mass, was lined with a necrotic, shreddy material, and had a capacity of about 400 cc. Microscopic examination of sections from the main body of the tumor and from the wall of the cyst disclosed a cellular structure not unlike the normal pancreas, the epithelial cells were arranged into acini and ductlike structures and there was little interparenchymal connective tissue (fig 4).

Cystadenocarcinoma.—Malignant cysts of the pancreas are likewise rare. Scott³² reported on a cystic tumor of the pancreas with lymphatic

32 Scott, G. Adeno-Cistoma papillefero del pancreas. Arch per le sc med, 1906, abstr, Centralbl f allg Path u path Anat 18 844 (Oct) 1907.

and pulmonary metastasis and implantations on the peritoneal surface. Hartman³ reported observations at necropsy in a case of malignant cystic tumor of the pancreas with metastasis to the liver.

Among the eighty-eight patients with pancreatic cyst treated surgically at the Mayo Clinic, there were four with carcinomatous cysts. In one case a large cystic tumor was found with nodules over its surface and nodules in the liver in the left side of the abdomen. Two of the nodules of the liver were excised and proved to be carcinoma. The surgeon thought that the cystic tumor originated in the pancreas. In the second case there was a cystic mass of the pancreas approximately 20 by 25 cm. Part of the mass removed at operation proved to

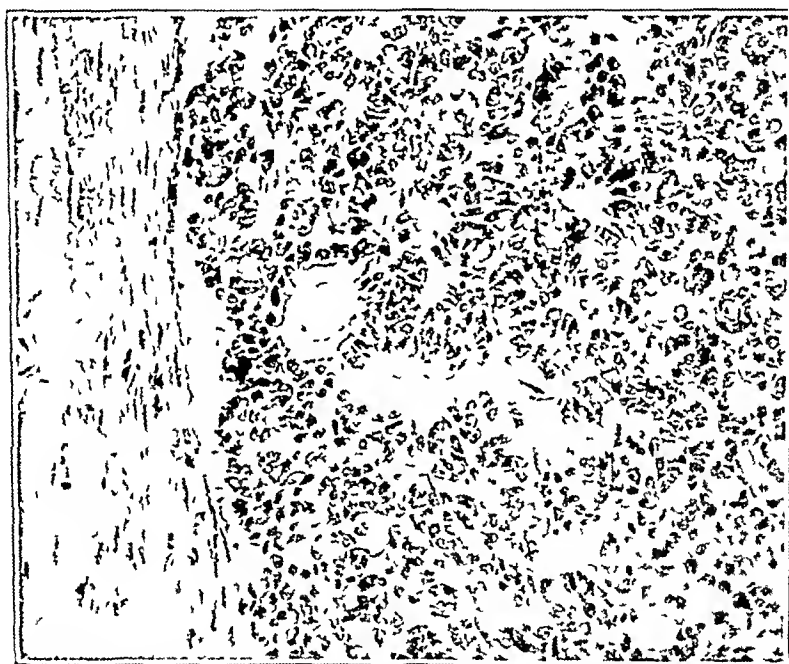


Fig. 4—Wall of cyst in cystadenoma of pancreas (hematoxylin and eosin, $\times 175$)

be benign. However, tissue removed from other cystic masses in the same pancreas was reported as cystadenocarcinoma. The patient recovered from the operation, but we have no further information concerning the case. In the third case a large cystic tumor was removed from the tail of the pancreas. The cyst contained about 4 liters of fluid, and its inner walls were irregular and lined with necrotic, shreddy tissue in which there were degenerated epithelial cells that appeared to be malignant. In one part of the mass was a solid tumor, the cyst was directly contiguous with it. Microscopically, the tumor was carcinoma of the pancreas. Part of the wall of the cyst was smooth externally

and consisted of connective tissue. In the fourth case, a pancreatic cyst was drained surgically, and the patient died following the operation. The surgeon made a note at the operation that the pancreas was very hard. At necropsy a cyst of about 10 cm in diameter was found in the lesser peritoneal cavity. It was filled with straw-colored fluid and was adherent to the pancreas, from the head to the tail. Carcinoma was found in the pancreas.

Teratomatous Cysts—Keir³⁴ reported a cyst, the wall of which he said was teratomatous. He did not give a detailed description of the histopathologic features.

CYSTS RESULTING FROM PARASITES

Cysts of the pancreas caused by parasites are rare. They are encysted forms of some of the parasites for which man is the intermediate host. We have seen only two types described, echinococcus cyst and *Cysticercus cellulosae*.

Hanser,³⁵ in 1912, reviewed twenty-eight cases of echinococcus cyst noted in the literature. Twenty-two of these were in the pancreas and six were in the vicinity of the pancreas. Seifarth,³⁶ in 1920, reviewed forty cases of echinococcus cyst of the pancreas.

The pathologic diagnosis rests on the finding of scolices or hooklets (Stitt,³⁷ Rivas³⁸). Echinococcus cysts may be very large. Raillet and Monot³⁹ stated that *Cysticercus cellulosae* have been found in the pancreas of man. Such cysts are small, about 15 by 7 mm in diameter, and contain the scolex and hooklets of *Taenia solium*.

GENERAL CHARACTERISTICS OF CYSTS OF THE PANCREAS

Shape—Very small cysts are spherical. Larger cysts are shaped by their surroundings. Extremely large cysts assume ameboid characteristics and may fill the entire abdomen. Certain cysts are multilocular (fig. 5), although they are rounded on the outside, they have many partially or completely separated spaces within.

34 Kerr, A. A. Cysts and Pseudocysts of the Pancreas, Surg. Gynec. Obst. **27** 40 (July) 1918.

35 Hanser, Robert. Ueber Echinokokken des Pankreas, Beitr. z. klin. Chir. **77** 360 1912.

36 Seifarth, Carl. Parasiten im Pankreas. Centralbl. f. Bakteriol. **85** 27 (Sept.) 1921.

37 Stitt, E. R. The Diagnostics and Treatment of Tropical Diseases, ed. 5. Philadelphia, P. Blakiston's Son & Company, 1929.

38 Rivas, Damaso. Human Parasitology. Philadelphia, W. B. Saunders Company, 1920.

39 Raillet and Monot. Ascaride dans le pancreas d'un process. Compt. rend. Soc. de biol. **45** 407 (April) 1893.

Size—The size of pancreatic cysts varies within wide limits. The largest one reported in the literature contained 20 liters of fluid¹⁹. Most of the cysts reported were large enough to be palpated through the abdominal wall. In one of the forty-seven cases that we reported it was estimated that 20 liters of fluid was present, in one case 8 liters of fluid was present, in one, 6 liters, in two, 4 liters each, and in two, 3 liters each. The smallest cyst for which operation was performed in our series was 6 cm. in diameter. It originated in the head of the



Fig 5—Multilocular simple cyst of the pancreas

pancreas and presented in the transverse mesocolon. The duct of Wüsting and the cyst both contained stones. Three other small cysts found in this series were 7, 8 and 9 cm. in diameter, respectively, and each was enucleated completely.

Very small cysts are sometimes found at necropsy (fig 6). In the necropsy records of the clinic we were able to find only twenty cases of cysts of the pancreas that had not been operated on. The small cysts

⁴⁰ Stapper Julius. Beiträge zur Diagnose der Pancreascysten. Bonn, Joseph Bach, 1892.

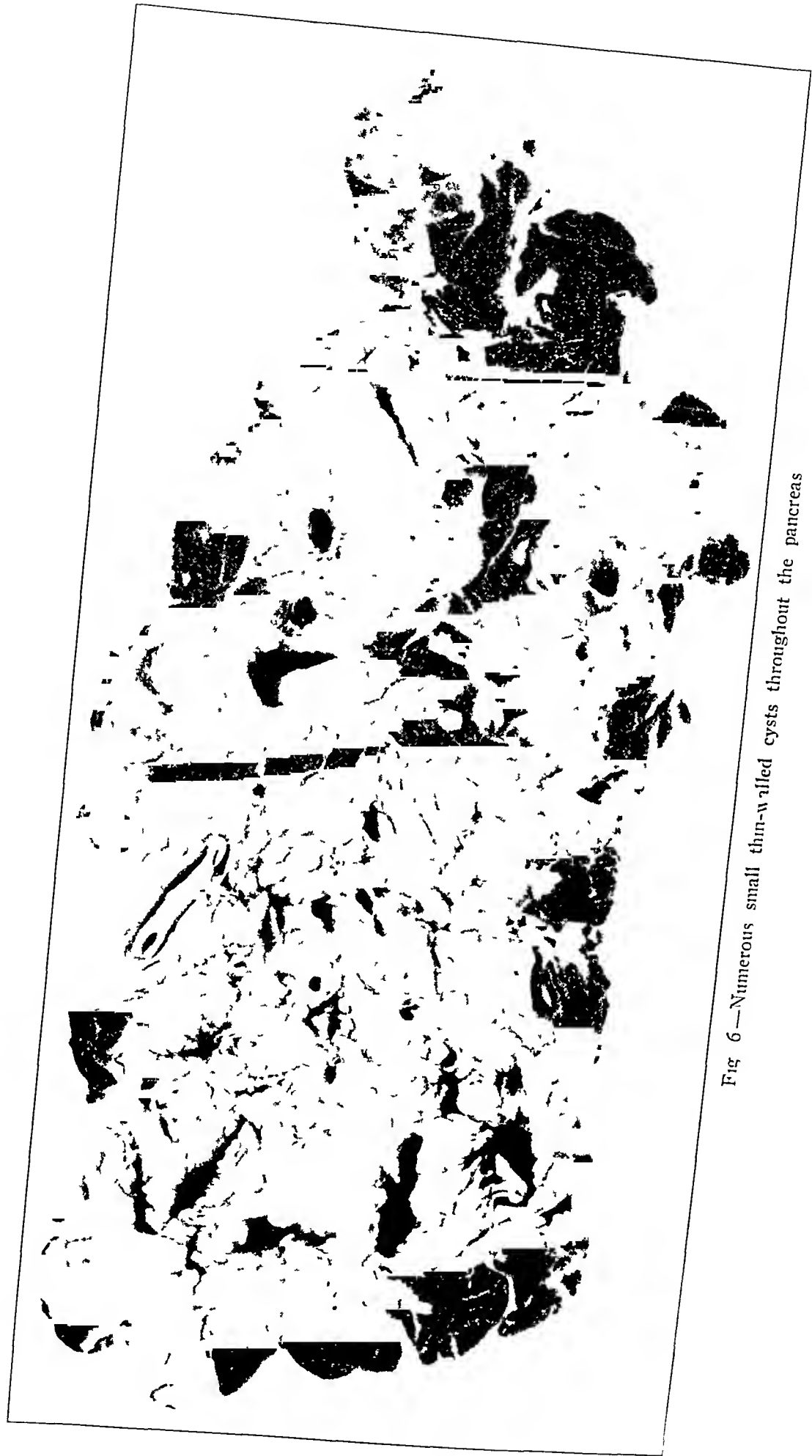


Fig 6—Numerous small thin-walled cysts throughout the pancreas

that were found at necropsy usually contained clear fluid, their walls were thin and microscopically consisted of connective tissue and an epithelial lining. It is of historic interest that Klebs⁴¹ gave the name "acne pancreatica" to cases in which the contents of the cysts had become mushy. Generally only a single layer of epithelial cells lines these cysts. They vary from the tall columnar (fig 7) to the flattened type. Sometimes there are little papillary projections into the cavity of the cyst (fig 8). Such projections do not indicate that the cyst itself is a neoplasm or that it is a cystadenoma.

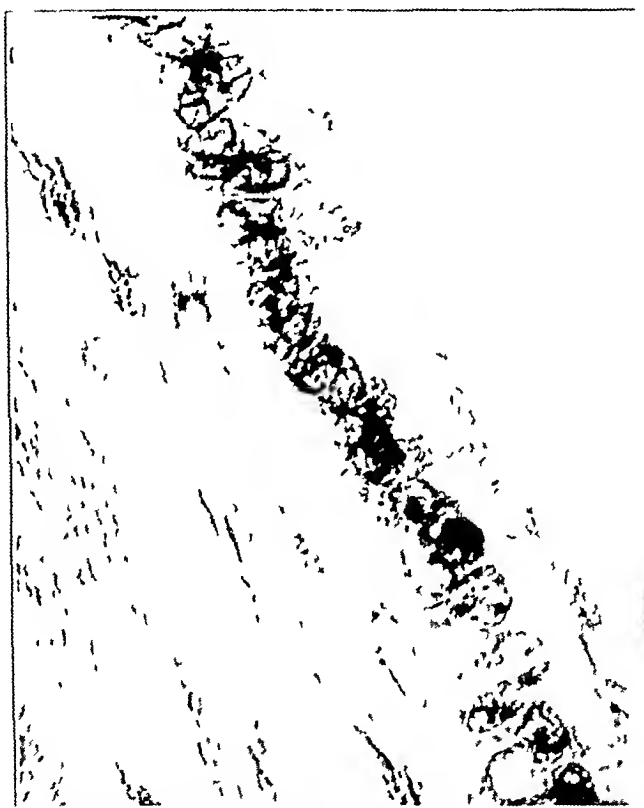


Fig 7—Columnar epithelial cells lining simple cyst of the pancreas ($\times 700$)

Number—In twelve of the twenty cases in our series that were noted at necropsy for which operation had not been performed, the cysts were multiple, in seven cases the cysts were single and in one case, multilocular. Our information concerning the number, type and pathologic change in the larger surgical cysts is limited, because extensive exploration frequently is impossible, and few cases come to necropsy.

Site—In the cases noted at necropsy four cysts were described as being confined to the tail of the pancreas (three single and one multiloc-

41 Klebs Edwin. Handbuch der pathologischen Anatomie, ed 2. Berlin: A Hirschwald, 1876.

ular) three were in the head only (two single and one multiple), and three were in the body (two single). In the remaining ten cases the cysts were found throughout the gland in two cases, in the head and body in two, and in the tail and body in one case, in five cases the site was not adequately described. This distribution of the cysts is not indicative of a place of predilection for pancreatic cysts. It was Lazarus' belief that the least common site was in the head of the pancreas because of the least likelihood of retention. Korte gave the site in forty-seven cases as follows: the head in sixteen cases, the body in seven, the body and tail in twelve and the tail in twelve.

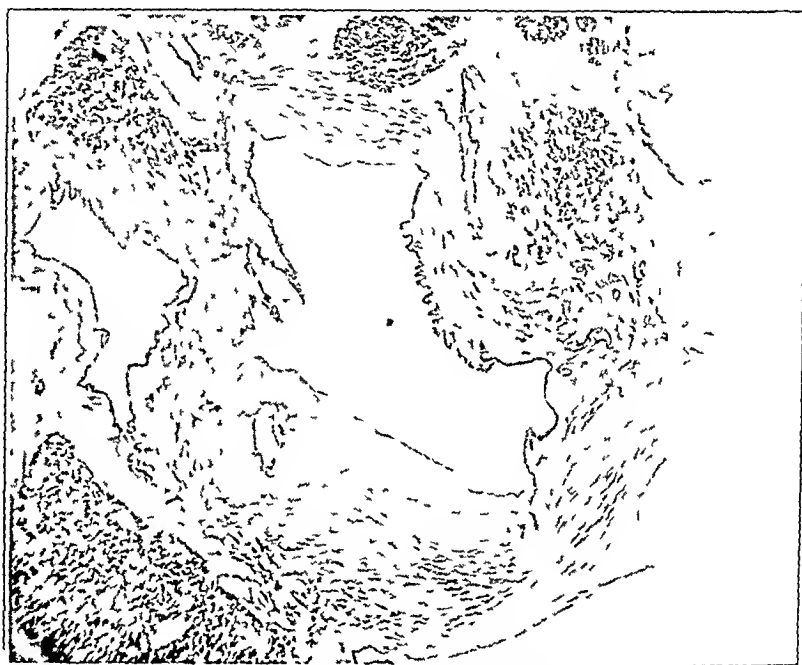


Fig 8—Simple cyst of pancreas, showing papillary projections (hematoxylin and eosin, $\times 20$)

Content—The gross appearance of the contents of pancreatic cysts is variable. The fluid was clear or amber-colored in only seven of our series of forty-seven cases. In fourteen cases it was chocolate-colored or blood-stained, and in nine cases the contents were described as cloudy fluid and gelatinous material, yellow milky fluid, thick, oily, bloody material, cloudy fluid, clear gelatinous fluid (subsequently thick mucilaginous and later milky), light-colored honey-like material, yellowish-green fluid, slightly turbid fluid, or greenish-black fluid. The appearance of the contents in the remaining seventeen cases was not described.

Sometimes the bloody appearance of a hemorrhagic cyst disappears, and the contents become clear fluid. Lazarus observed this in his experimentally produced cyst, and this seems to have taken place in one of the

cases in our series in which the condition followed trauma. The patient was a man, aged 27, who had suffered a blow in the abdomen in an automobile accident five months before admission. He was operated on, and a cyst of the pancreas was found which was estimated to be 24 cm in diameter and to contain about 800 cc of a straw-colored fluid. It had been aspirated five times before he came to the clinic. Amber-colored fluid was removed each time. Histologic examination of the walls of cysts sometimes shows a blood pigment which indicates their hemorrhagic origin, whether or not their contents are clear. Dermoid cysts of the pancreas, like those in other parts of the body, contain a gumous, cheesy material and hair, and they may even contain teeth. Degenerated and necrotic tissue may sometimes be found in cysts, and even portions of the pancreas.⁴²

Microscopically, cysts may contain epithelial cells, erythrocytes, leukocytes, globules of fat, crystals of fatty acids, cholesterol, hematin crystals and necrotic tissue.⁴³ Serum albumin, serum globulin, mucin, peptone, hemoglobin, leucine, tyrosine and sugar also have been found.⁴⁴ The reaction usually is alkaline. The content of a cyst removed by Bozeman⁴⁵ and described by Garrigues⁴⁶ was acid. The specific gravity varies from 1.007 (Tremanne)⁴⁷ and 1.009 (Morton)⁴⁸ to 1.060, which is that of blood. Ferments are often present. In the fluids in sixty-six cases in Korte's series, in which the contents were analyzed in this regard, twelve were found not to contain ferments, twenty were found to contain one ferment (fourteen starch-splitting, three fat-splitting, and three protein-splitting), twenty were found to contain two ferments (sugar and fat, fourteen; sugar and protein, four; and fat and protein, two), and fourteen were found to contain three ferments. The presence of a starch-splitting ferment is not pathognomonic of pancreatic cysts, since either isolated or free fluids in the abdominal cavity may contain it.⁴⁹

42 Lloyd (footnote 16) Israel (footnote 27)

43 Lazarus (footnote 4) Opie (footnote 6) Oser Leopold. Diseases of the Pancreas, in Nothnagel. Encyclopedia, Philadelphia, W. B. Saunders Company, 1903, pp 17-270. Pepper William. Tumour of the Head of the Pancreas. *Am J M Sc* **61** 159 (Oct) 1871.

44 Lazarus (footnote 4) Korte (footnote 18)

45 Bozeman, N. Removal of a Cyst of the Pancreas Weighing Twenty and One-Half Pounds, *Med Rec* **21** 46 (Jan) 1882.

46 Garrigues, H. J. The Anatomy and Histology of Cyst of the Pancreas. *Med Rec* **21** 286 (March) 1882.

47 Tremanne, W. S. Cyst of the Pancreas Successfully Removed, *Tr Am Surg A* **6** 557, 1888.

48 Morton B. B. A Case of Pancreatic Cyst Associated with Glycosuria and Gallstones. Necropsy, *Lancet* **1** 242 (Jan) 1897.

49 von Jaksch R. Ueber das Vorkommen von Fermenten in den Faces der Kinder, nebst Bemerkungen über das Vorkommen von saccharificierenden Fermenten in Cysteninhalt. *Ztschr f phys Chem* **12** 116, 1888.

ETHYLENE ANESTHESIA

ANALYSIS OF REBREATHED MIXTURES¹

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The carbon dioxide filter in inhalation anesthesia has been in use for several years, and analysis of the rebreathed gases has been made by F T Rombeiger and others on mixtures in which ether was used. However, no data have been published on patients in whom ethylene-nitrous oxide-oxygen anesthesia, without ether, has been used. The following preliminary report on a small series of cases is submitted in order to call attention to the possibility of inducing anesthesia with ethylene and maintaining surgical relaxation without giving additional anesthetic agents, after the introduction of a filter that removes carbon dioxide from the expired gases. Such a method is apparently without danger, and brings about a large reduction in the cost of the anesthetic agents.

ANALYSIS OF REBREATHED MIXTURES

In a series of seven cases, analyses were made on the contents of the rebreathing bag during the progress of the anesthesia. For each case at least seven samples, and in some eight, were taken at intervals of five or seven minutes. These samples were drawn directly from the rebreathing bag into sample tubes over mercury. The tubes were of approximately 25 cc volume and were closed at one end by a ground glass stopcock and at the other by a column of mercury, the height of which could be regulated by raising or lowering a reservoir of mercury. In each sample, the concentrations of oxygen, carbon dioxide and ethylene were determined by analysis, and the relative nitrous oxide concentration determined by subtracting the sum of the three from 100 per cent. In each instance, a completely closed system made this computation possible. No samples were taken until the patient had been under the anesthetic for at least ten minutes, it was estimated that at this time all nitrogen had been removed from the expired gases.

The method of analysis was that of Haldane and Henderson, in which a known amount of gas is passed repeatedly from a calibrated buret into the absorbing solutions and returned to the buret until a constant reading is attained. This transfer is accompanied by means of a reservoir of mercury which is raised or lowered at will. The absorbents used were sodium hydroxide for carbon dioxide,

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potassium pyrogallate for oxygen and in some cases, bromine water, and in others, 20 per cent silver nitrate, for ethylene. In these cases the carbon dioxide filter was used. In these cases the filter was cut in. When the filter was not used, the patient received this mixture throughout the course of the anesthesia. After the filter had been cut in, patients were carried on the contents of the rebreathing bag alone for from one hour and twenty minutes to one hour and twenty minutes. This oxygen and only sufficient oxygen was given to keep the bag inflated so that at no time was the rebreathing bag allowed to become deflated. These patients, although they received no additional anesthetic, evidenced perfect surgical anesthesia with better relaxation than those with whom the filter was not used. This observation held true for a large number of patients with whom the carbon dioxide filter was not used and in whom anesthesia was induced and maintained by means of a continuous supply of the mixture of 40 per cent

TABLE 1—Results of Analysis of Rebreathed Mixture in Case 1

Sample	O ₂	CO ₂	C.H ₄	N ₂ O
1	20.80	0.00	18.00	67.30
2	25.85	0.75	37.00	36.10
3	29.80	0.70	40.50	29.00
4	34.00	0.60	29.00	36.10
5	42.50	0.50	25.00	32.00
6	47.00	0.65	23.50	28.85
7	49.75	0.35	22.50	27.40

ethylene, 40 per cent nitrous oxide and 20 per cent oxygen, it was impossible to keep surgical relaxation by the administration of oxygen alone.

CASE 1—A woman aged 27, weighing 110 pounds (49.9 Kg.), was subjected to the following operations: curettage of the uterus, cauterization of the cervix, myomectomy and appendectomy. The preparation included pantopon, one-sixth gram (0.01 Gm.), scopolamine, one four-hundredth gram (0.00016 Gm.) injected one hour before operation and repeated in thirty minutes, and procaine hydrochloride, 1 per cent, injected into the fascia and muscles. Anesthesia was started at 9:48, and the mixture was "40-40-20." The filter was cut in at 10:13. The first sample was taken at 10:13. Samples were taken every five minutes. For twenty-five minutes, 400 cc of oxygen per minute was given, and 350 cc per minute for the remainder of the time. The results of the analysis of the rebreathed mixture are given in table 1. Respirations were 20 per minute. The pulse rate was 72.

CASE 2—A man, aged 38, weighing 220 pounds (99.7 Kg.), underwent appendectomy. In preparation, he was given pantopon, one-sixth gram, and scopolamine, one four-hundredth gram, one hour before operation with repetition of the injections in thirty minutes. Anesthesia was started at 10:46, and the mixture was "40-40-20." The filter was cut in at 10:54. The first sample (tube) was taken at 10:54. Samples were taken every seven minutes, alternately from exhaling tube and bag. For the first two samples, 400 cc of oxygen per minute was given; 600 cc for the next four samples; 550 cc for the last two samples. The results of the analysis of the samples are given in table 2.

The pulse rate was 72 The respirations were 20 per minute The blood pressure was systolic, 126, diastolic, 88 The skin was wet

CASE 3—In case 3, the filter was not used A man, aged 21, weighing 142 pounds (64.4 Kg), was operated on for excision of varicose veins of the spermatic cord The preparation consisted of morphine, one-sixth gram, and scopolamine, one six-hundredth gram (0.0001 Gm) one hour before operation, the injection being repeated in thirty minutes Anesthesia was started at 8.05 Samples were taken every five minutes The mixture was "40-40-20" Eleven per cent oxygen

TABLE 2—Results of Analysis of Rebreathed Mixture in Case 2

Sample	O ₂	CO ₂	C ₂ H ₄	N ₂ O
1	15.00	2.30	52.00	30.70
2	20.00	3.50	7.00	69.50
3	25.00	2.40	41.00	31.60
4	27.00	0.20	27.00	45.30
5	36.00	1.70	27.50	34.80
6	38.00	0.55	27.00	34.15
7	42.50	3.05	20.00	33.45
8	47.00	0.50	18.00	34.50

TABLE 3—Results of Analysis of Rebreathed Mixture in Case 3

Sample	O ₂	CO ₂	C ₂ H ₄	N ₂ O
1	20.00	0.60	42.00	37.40
2	20.00	1.20	41.50	37.30
3	20.00	0.65	42.00	37.35
4	22.00	0.60	42.00	35.40
5	21.00	1.00	53.50	24.50
6	20.00	1.00	53.50	25.50
7	21.50	0.90	53.50	24.10
8	21.50	0.70	53.50	24.30

TABLE 4—Results of Analysis of Rebreathed Mixture in Case 4

Sample	O ₂	CO ₂	C ₂ H ₄	N ₂ O
1	17.00	3.60	56.50	22.90
2	16.00	0.40	56.50	27.10
3	15.00	3.50	63.00	18.50
4	16.50	0.85	52.50	30.15
5	20.00	0.25	50.00	29.75
6	18.50	1.90	50.00	29.60
7	18.00	0.25	57.50	24.25
8	18.50	0.20	52.50	28.80

was given during the first five minutes 20 per cent oxygen during the remainder The results of the analysis of the samples are recorded in table 3

The pulse rate was 68, the respiratory rate was 16 The blood pressure was systolic 112 diastolic, 70 The skin was dry

CASE 4—A man, aged 19 weighing 170 pounds (77.1 Kg), was operated on for closure of a colostomy In preparation, morphine one-sixth gram and scopolamine, one four-hundredth gram, were given one hour preoperatively and repeated in forty minutes Anesthesia was started at 9.41 and the mixture was "41-41-18" The filter was cut in at 9.54 The first sample (ex tube) was taken at 9.54 Samples were taken every seven minutes alternately from exhaling and inhaling tube Eighteen per cent oxygen was used for induction and 400 cc of oxygen per minute after the filter was cut in

The patient was frightened and excited before the induction of anesthesia. The pulse rate was from 116 to 160, the respirations numbered from 20 to 24 per minute. The blood pressure was systolic, 114, diastolic, 68.

CASE 5—In case 5, the filter was not used. A woman, aged 30, weighing 110 pounds (49.9 Kg), underwent the following operations: Dilation and curettage of the uterus, cauterization of the cervix, a Baldy-Webster suspension, resection of a cyst of the left ovary, and appendectomy. The preparation consisted of pantopon, one-sixth grain, and scopolamine, one four-hundredth grain, given one hour preoperatively and repeated in thirty minutes. Anesthesia was started at 9 30. The first sample was taken at 9 52. Samples were taken every five minutes. The mixture was 90 per cent nitrous oxide and 10 per cent oxygen for the first eighteen minutes, 500 cc each of ethylene, nitrous oxide and oxygen per minute for the remainder of the anesthesia. The results of the analysis of the samples are given in table 5.

TABLE 5—Results of Analysis of Rebreathed Mixture in Case 5

Sample	O ₂	CO ₂	C ₂ H ₄	N ₂ O
1	20 00	2 00	43 00	35 00
2	20 50	2 00	55 50	22 00
3	21 50	1 50	54 50	22 50
4	21 50	1 10	53 50	23 90
5	22 00	1 10	40 00	37 40
6	22 00	1 50	50 00	26 50
7	22 00	1 25	55 00	21 75
8	22 00	1 55	54 50	21 95

TABLE 6—Results of Analysis of Rebreathed Mixture in Case 6

Sample	O ₂	CO ₂	C ₂ H ₄	N ₂ O
1	14 00	1 50	51 00	33 50
2	17 50	0 40	47 50	34 60
3	16 50	0 40	56 50	26 60
4	16 50	0 30	55 50	37 70
5	15 00	0 45	55 50	29 05
6	19 50	0 20	43 00	37 30
7	21 00	0 85	39 50	38 65
8				

The pulse rate was from 88 to 100, the respirations were from 12 to 16 per minute. The blood pressure was systolic, 110, diastolic, 70. The respirations increased in volume, but not in rate.

CASE 6—A man, aged 33, weighing 160 pounds (72.6 Kg), underwent appendectomy. In preparation, he was given pantopon, one-sixth grain, and scopolamine, one four-hundredth grain, at 7 15, and the injections were repeated at 8 30. Anesthesia was started at 9 15, and the mixture was 2 liters (2,000 cc) each of nitrous oxide and ethylene and 1,000 cc of oxygen per minute. The filter was cut in at 9 27. The first sample was taken at 9 27. Samples were taken every five minutes. From 9 27 on, 450 cc of oxygen was used. The results of the analysis of the samples are given in table 6.

The patient was maintained in good condition, with no variation. The pulse rate was 80, the respiration rate, 28.

CASE 7—A woman aged 26, weighing 104 pounds (47.2 Kg), underwent the following operations: lysis of pelvic adhesions and resection of an ovarian cyst. The preparation consisted of pantopon one-sixth grain and scopolamine, one

four-hundredth grain Anesthesia was started at 9 09, and the mixture was "42-42-16" The operation was begun at 9 20 The filter was cut in at 9 25, using 400 cc of oxygen per minute The first sample was taken at 9 25 Samples were taken every five minutes The results of the analysis of the samples are given in table 7

The condition of the patient was good One per cent procaine hydrochloride was injected into the fascia and rectus muscle The pulse rate was from 75 to 100, the respirations were from 15 to 20 per minute The blood pressure was systolic, 100, diastolic, 70

COMMENT

A comparison of the gases in those cases in which the filter was not used with those in cases in which it was used shows marked difference in concentration In the former, the oxygen concentration remained relatively constant at approximately the induction percentage, while in the latter there was a gradual rise or accumulation of oxygen This increase was as high as 49 per cent in sample 8 of case 1 and 47 per cent

TABLE 7—*Results of Analysis of Rebreathed Mixture in Case 7*

Sample	O ₂	CO ₂	C ₂ H ₄	N ₂ O
1	17 00	0 25	47 50	35 25
2	24 50	0 20	47 80	27 50
3	24 50	0 20	47 80	27 50
4	24 50	0 10	7 00	68 40
5	22 50	0 50	5 00	72 00
6	24 50	0 18	4 60	70 72
7	45 40	0 01	39 80	14 79

in case 2 It is doubtful that the amounts of oxygen fed were responsible for such an increase, as the bag would empty rapidly if a reduction of a few cubic centimeters was made In the cases in which the filter was used, the difference between the percentage of oxygen administered and the amount recovered from the rebreathing bag on analysis was far out of proportion to the metabolic rate of the patient The least amount that could possibly be used in any case was 350 cc per minute, while in case 2, 600 cc was necessary The average amount administered was between 400 and 500 cc

In many samples in cases 3 and 5, in which the filter was not used, the carbon dioxide concentrations were lower than in case 2, in which the filter was used This apparent discrepancy is easily explained by the fact that in case 2 alternate samples were drawn from the exhaling tube As would be expected, these samples show high concentrations of carbon dioxide, but little variation of the other gases present

In cases in which the filter was not used, the average ethylene concentration was higher than the nitrous oxide concentration, but in cases in which the filter was used the reverse was true This seems to indicate

that nitrous oxide was preferred in the former, whereas ethylene was preferred in the latter

The economical feature of this method including the use of a filter is evident. A patient consuming 800 cc each of nitrous oxide and ethylene per minute and carried for an hour and a half with no additional anesthetic would represent a saving of 81,000 cc each of ethylene and nitrous oxide gas ¹

1 Additional work is in progress in which analysis is being made of the ethylene, nitrous oxide, oxygen and carbon dioxide content of venous and of arterial blood during the course of the anesthesia. These are in conjunction with similar analyses of the rebreathed gases.

THE EFFECT OF SPINAL ANESTHESIA ON ARTERIAL TONE¹

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In a previous study¹ it was shown that the cardiac output in dogs under spinal anesthesia remained at a nearly normal level unless a marked diminution in blood pressure took place. The decrease in blood pressure came first and was usually of greater degree than the later decrease in the output of the heart. This sequence of events is just the opposite of that found in experimental traumatic shock and experimental hemorrhage². It was believed that a further comparison of these states might throw light on the nature of the different types of shock. These subjects have received a great deal of study in the past fifteen years, but, so far as one can judge from the literature, many of our concepts as to their exact nature are vague and incomplete.

METHOD

Dogs were used. They received barbital (0.3 Gm per kilogram) intravenously from one to two hours before the experiments were begun. Blood pressure was measured by means of a mercury manometer connected with a cannula in the carotid artery. Spinal puncture was done as previously described by us. The animals received spinocaine (a proprietary procaine preparation) from 1 to 3 cc,³ depending on the size of the dog and the height of the anesthesia desired.

Arterial tone was measured by means of recording inflow into the selected artery. This vessel—the femoral, the brachial or the carotid artery—was exposed for a distance of from 10 to 20 cm, care being taken not to injure the branches. The distal end of the exposed vessel was then cannulated, the cannula pointing toward the heart. A bull-dog clamp was placed on the artery first. The cannula was connected to a metal coil, which was immersed in a water bath the temperature of which was kept at 38 to 40 C. To the other end of the coil was attached a rubber tube, which was connected with an ordinary 50 cc buret that was kept at

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* From the Departments of Gynecology and Medicine of Vanderbilt University

1 Burch, J. C., and Harrison, T. R. The Effect of Spinal Anesthesia on the Cardiac Output, *Arch Surg* **21** 330 (Aug) 1930

2 Blalock, A. Mechanism and Treatment of Experimental Shock, Shock Following Hemorrhage, *Arch Surg* **15** 762 (Nov) 1927

3 Pitkin, G. P. Controllable Spinal Anaesthesia "Spinocaine," *Brit J Anaesth* **6** 22, 1928

a height of 2 meters above the table on which the animal was prepared. The system was filled with a warm saline solution, care being taken to expel all the air. When a measurement of perfusion rate was to be made, the clamp at the end of the cannula was removed, and simultaneously a second bull-dog clamp was placed on the artery at the proximal point of exposure. Care was taken to be certain that this proximal clamp was always placed at the same point on the artery. In large dogs the inflow period was fifteen seconds, in small dogs, because of the lesser inflow, periods of thirty seconds were employed. This method is similar to that employed by Cattell.⁴

The advantage of this reverse perfusion method that we have used consists primarily in the fact that at all times, except during the relatively few seconds of the perfusion periods, the perfused tissues are receiving a normal blood supply. Forward perfusion methods involve the disadvantage of ischemia in the tissues to be studied, and it is well known that lack of oxygen may cause changes in vascular caliber.⁵

TABLE 1—*The Effect of Spinal Anesthesia on the Perfusion Rate*

Experiment Number	Average Perfusion Rate, Cubic Centimeters per Minute		Region Perfused
	Before Spinal Anesthesia	After Spinal Anesthesia	
29	66	94	Hind leg
31	88	104	Hind leg
32	49	145	Hind leg
44	60	100	Hind leg
46	67	50	Hind leg
33	15	28	Fore leg
36	19	44	Fore leg
34	92	95	Head
35	104	120	Head

In every instance several measurements of inflow were made. The values expressed in the tables are the averages of from three to five determinations and for convenience of comparison are expressed in terms of cubic centimeters per minute. Ordinarily, duplicate or triplicate measurements agreed fairly well, although considerable variations were observed in dogs with rhythmic fluctuations in blood pressure, it is thought that these variations represent changes in vaso-motor tone.

RESULTS

The effect of spinal anesthesia on the perfusion rate is shown in table 1. In the first five of these experiments the anesthetized area, i. e., the posterior extremity, was perfused. In four of these marked increases in perfusion rate varying from 20 to 200 per cent were noted. In the fifth experiment, a diminution of about 25 per cent was found. We are unable to explain this exceptional observation.

4 Cattell, McKeen. Studies in Experimental Traumatic Shock. Action of Ether on Circulation in Traumatic Shock, Arch Surg 6:69 (Jan) 1923.

5 Krogh, A. The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1924.

Contrary to our expectations, it was found that the perfusion rate in the unanesthetized areas was also usually increased after spinal anesthesia. Presumably, this change is to be attributed to a slight diffusion toward the head of the anesthetic solution. It would appear that the vasomotor fibers are especially sensitive to the action of the anesthetic.

The observations reported in table 2 are of especial interest. In these animals a progressive drop in blood pressure was produced by repeated bleedings, and perfusion rates were measured at intervals throughout the experiments. In the first two experiments, the dogs

TABLE 2—*The Effect of Hemorrhage on the Perfusion Rate*

Experiment Number	Before Hemorrhage		After Hemorrhage		Comment
	Mean Blood Pressure, Millimeters of Mercury	Perfusion Rate, Cubic Centimeters per Minute	Mean Blood Pressure, Millimeters of Mercury	Perfusion Rate, Cubic Centimeters per Minute	
42	138	49	120	35	No spinal anesthesia, hind leg perfused
			40	20	
			40	50	
			22	75	
			0	85	
43	118	160	104	80	No spinal anesthesia, hind leg perfused
			42	135	
			38	130	
			24	104	
32	52	144	38	141	Spinal anesthesia, hind leg perfused
44	82	100	90	96	Spinal anesthesia, hind leg perfused
			84	130	
			76	130	
			48	100	
46	94	46	76	46	Spinal anesthesia, hind leg perfused
			39	45	

had not received spinocaine. In each instance the initial hemorrhage was followed by a marked diminution in the perfusion rate, indicating arterial constriction. After the blood pressure had become very low—40 mm of mercury or less—the perfusion rate increased toward or beyond the normal. It appears therefore that the initial effect of diminished blood volume is to cause a compensatory increase in vasomotor tone, but that after the blood pressure has fallen well below the critical level,⁶ the vasoconstrictor center suffering from impaired blood supply becomes weakened, loses its tone, and as death approaches, the perfusion rate rises.

The last three experiments in table 2 were made on animals that had received spinocaine before they were bled. In these animals the

⁶ Cannon, W. B. and Cattell, McK. Experimental Traumatic Shock. Critical Level in Falling Blood Pressure, Arch Surg 4:300 (March) 1922.

perfusion rate was unchanged or increased by hemorrhage. The normal initial vasoconstrictor response to hemorrhage was absent. As this vasoconstrictor response is probably compensatory in nature, it becomes clear why experimental animals and patients under spinal anesthesia react so poorly to hemorrhage.⁷ The normal subject is able to compensate, in part at least, for diminution in blood volume by active constriction of the arteries to the less vital organs. Such organs thereby suffer from a decreased blood supply,⁸ but the blood pressure remains fairly well up, and circulation to the vital organs is maintained despite the marked diminution in cardiac output.⁹ In subjects under spinal anesthesia, the power of active vasoconstriction is, however, more or less completely absent because of the paralysis of vasomotor fibers, and loss of a relatively small amount of blood is fatal.

COMMENT

It is believed that the studies reported in this paper may have a significance beyond the light they throw on the physiology of spinal anesthesia. Clinically, one observes two different kinds of traumatic shock which are confusing because they so often occur simultaneously. The more important and more serious of these is the so-called secondary shock, which occurs some minutes or some hours after injury. The recent researches of Blalock and his co-workers seem to show beyond question that local loss of blood plasma or of whole blood accounts in large measure for the phenomena observed in this type of shock, which is characterized by diminished blood volume, an early fall in cardiac output, a relatively late fall in mean arterial pressure and, presumably at least, by an initial and compensatory increase in vasomotor tone. The primary physiologic disturbance in this condition seems to be diminished blood volume.

Primary traumatic shock or collapse is quite different. It comes on immediately after injury and is presumably of reflex origin. The drop in blood pressure occurring immediately after a gunshot wound and that following trauma to the central nervous system presumably represent types of primary shock. The decrease in blood pressure in

7 Burch, J., Harrison, T. R., and Blalock, A. Comparison of the Effects of Hemorrhage in Dogs Under Ether and Under Spinal Anesthesia, *Arch Surg*, in press

8 Gesell, R. Factors Controlling Volume-Flow of Blood, *Am J Physiol* **47** 428, 1919

9 Blalock, A. Regulation of Circulation, Relative Importance of Nervous Endocrine and Vascular Regulation in Response of Cardiac Output to Anoxemia *Am J Physiol* **83** 284 1927

subjects under spinal anesthesia appears to belong to this group. If so, primary shock is characterized by an initial decrease in vasomotor tone with an early drop in blood pressure and a relatively late decrease in cardiac output, the blood volume being unaffected. In order to classify our concepts, it might be well to speak of neurogenic (rather than primary) and hematogenic (rather than secondary) shock.

SUMMARY

A method for the study of arterial tone by reverse arterial perfusion has been described.

A normal animal responds to hemorrhage by an initial vasoconstriction.

After the blood pressure has fallen below 40 mm, vasodilatation occurs, and death soon follows.

Spinal anesthesia is usually followed by a marked vasodilatation. This may involve the unanesthetized as well as the anesthetized areas.

The constrictor response to hemorrhage is abolished by spinal anesthesia, and it is believed that this observation explains the unusual susceptibility to hemorrhage of patients and animals under spinal anesthesia.

The bearing of these observations on current conceptions of shock has been discussed, and the suggestion has been made that the terms neurogenic and hematogenic be substituted for primary and secondary shock, respectively.

THE EFFECT OF THE ADMINISTRATION OF FLUID ON THE FALL IN BLOOD PRESSURE CAUSED BY SPINAL ANESTHESIA^{*}

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Our previous studies¹ have dealt with the physiologic changes in the circulation caused by spinal anesthesia. The present and subsequent studies are concerned with the treatment, and more particularly with the prevention, of the untoward effects. Of these effects, the fall in blood pressure is the most important, because it is the most common. In other types of low blood pressure the therapeutic value of large amounts of fluid is well recognized. Consequently, the effect of fluid has been studied first.

The methods employed have been discussed in some detail in the previous papers and need not be presented here. The amount of spino-caine (a proprietary procaine preparation) used varied from 0.5 to 2 cc, depending on the size of the dogs. All of the animals received barbital from one to two hours before the spinal puncture. The blood pressure was recorded from the carotid artery.

In table 1 are presented the observations on a series of dogs that received no fluid. The smallest percentage drop in blood pressure was 28, the greatest, 70, and the average, 41. Animals that had received small amounts, i. e., from 2 to 7 cc per kilogram of body weight of physiologic solution of sodium chloride intravenously showed similar changes (table 2). In this group the smallest drop in mean arterial pressure was 27 per cent, the greatest, 70 per cent, and the average 42 per cent. One may therefore conclude that such small intravenous infusions are of no value in preventing the diminution in blood pressure.

However, when larger amounts of saline solution were given, a beneficial effect was noted (table 3). In this group of animals that

^{*} Submitted for publication, July 3, 1930.

^{*} From the Departments of Gynecology and Medicine of Vanderbilt University.

1 Burch, J. C., and Harrison, T. R. The Effect of Spinal Anesthesia on Arterial tone, *Arch Surg*, this issue, p 1040, Burch, J. C., Harrison, T. R., and Block, A. Comparison of the Effects of Hemorrhage under Ether Anesthesia and under Spinal Anesthesia, *ibid* 21 693 (Oct) 1930, Burch, J. C., and Harrison, T. R. Effect of Spinal Anesthesia on Cardiac Output, *ibid* 21 330 (Aug) 1930.

received from 13 to 20 cc of physiologic solution of sodium chloride per kilogram of body weight, the smallest decrease in blood pressure was 8 per cent, the greatest 27 per cent and the average 19 per cent

TABLE 1—*Control Experiment The Effect of Spinocaine on the Blood Pressure of Dogs Receiving no Fluid*

Experiment Number	Amount of Fluid Administered, Cubic Centimeters per Kilogram	Mean Arterial Pressure Before Spinocaine, Millimeters of Mercury	Mean Arterial Pressure After Spinocaine, Millimeters of Mercury	Change in Mean Arterial Pressure, per Cent
3	0	84	60	—29
5	0	138	90	—31
7	0	108	66	—39
8	0	120	70	—42
10	0	100	66	—34
11	0	104	462	—58
12	0	116	84	—28
13	0	114	34	—70

Average arterial pressure before spinocaine, 110 mm of mercury, after spinocaine, 65 mm, average diminution in arterial pressure after spinocaine, 41 per cent

TABLE 2—*The Effect of Spinocaine on the Blood Pressure of Dogs Receiving Small Amounts of Solution of Sodium Chloride Intravenously*

Experiment Number	Amount of Fluid Administered, Cubic Centimeters per Kilogram	Mean Arterial Pressure Before Spinocaine, Millimeters of Mercury	Mean Arterial Pressure After Spinocaine, Millimeters of Mercury	Change in Mean Arterial Pressure, per Cent
33	2	108	32	—70
36	4	158	114	—28
45	6	95	70	—27
32	6	102	50	—51
34	7	90	60	—33

Average arterial pressure before spinocaine, 110 mm of mercury, after spinocaine, 65 mm, average diminution in arterial pressure after spinocaine, 42 per cent

TABLE 3—*The Effect of Spinocaine on the Blood Pressure of Dogs Receiving Large Amounts of Solution of Sodium Chloride Intravenously*

Experiment Number	Amount of Fluid Administered, Cubic Centimeters per Kilogram	Mean Arterial Pressure Before Spinocaine, Millimeters of Mercury	Mean Arterial Pressure After Spinocaine, Millimeters of Mercury	Change in Mean Arterial Pressure, per Cent
46	13	106	98	—8
31	14	116	88	—24
44	14	98	82	—16
34	16	98	72	—26
29	20	140	102	—27

Average arterial pressure before spinocaine 112 mm of mercury, after spinocaine, 90 mm average diminution in arterial pressure after spinocaine 19 per cent

The experiments seem to show clearly that the administration of salt solution, intravenously, immediately prior to the induction of spinal anesthesia, may be of value in preventing the drop in blood pressure, provided sufficient salt solution is given. One liter should constitute an adequate amount for an adult patient of average size.

FORTY-FOURTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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(Concluded from p 874)

MISCELLANEOUS

Injury of the Serratus Magnus Muscle—Fitchet⁴⁵ reported five cases of injury of the serratus magnus muscle. A winged scapula and an ability to invaginate the overlying skin into the subscapular space, together with persistent pain, a drooping shoulder and an inability to elevate the arm above the right angle, were the signs on which the diagnosis had to be made. The prognosis was good with early treatment.

Gaucher's Disease—The roentgenologic changes in the bones in Gaucher's disease were described by Kirklin and Hefke.⁴⁶ In the patient whom they had studied, changes were found in the long bones only. There was a generalized osteoporosis with thinned cortex similar to senile atrophy of the bone. There were also localized areas of destruction in the shafts of the long bones. The authors discussed the disturbance in lipid metabolism with the liberation of kersasin which was taken up by cells of the reticulo-endothelial system. The atrophy and localized areas of destruction were due to the invasion of the bone marrow by these cells. A review of the literature was appended.

⁴⁵ Fitchet S M. New England J Med 203 818 1930

⁴⁶ Kirklin B R and Hefke H W. Am J Roentgenol 24 258 1930

Lesions of the Bone in Tardive Heredisyphilis—Pendergrass, Gilman and Castleton⁴⁷ recorded a case of hereditary syphilis in which lesions of the bones became manifest during the third decade of life. No diagnosis had been made before this and no treatment had been given. In this case practically every known type of syphilitic lesion of the bone was present. There were increased density of the skull, osteomyelitis of the jaw, cystic degeneration of the upper end of the humerus, atrophic and hypertrophic changes at the elbow, gummas, destruction of cartilage at the hips and knees, coxa vara and effusion into the joints of both knees. Improvement followed antisyphilitic treatment.

Ganglion—McEvedy⁴⁸ advocated the treatment of ganglions by injection. After aspirating the contents or expressing them through the needle, from 0.5 to 2 cc. of a 5 per cent solution of sodium morrhuate was injected into the ganglion. There was mild pain for a day or two. In two weeks the ganglion should have disappeared. McEvedy reported ten cases, eight of which were cured, the two failures being due, in his opinion, to too small a dose.

BONE, JOINT AND TENDON SURGERY

Pain in the Lower Part of the Back—Campbell⁴⁹ stated that he had performed lumbosacral or sacro-iliac arthrodesis in 63 patients with the following conditions: infection, 35, trauma, 11, congenital anomalies, 3, benign tumors, 1, and tuberculosis, 13. For the lumbosacral fusion he utilized a curved graft removed from the posterior iliac crest, and for fusion of the sacro-iliac joint he employed an extra-articular operation performed by fusing adjacent portions of the sacrum and ilium and packing bone chips between them.

Technic of the Bony Shelf Operation in Congenital Dislocation of the Hip—Soutter⁵⁰ suggested a method of creating a bony shelf over the head of the femur in patients with an old irreducible congenital dislocation of the hip and also in those with an extremely shallow acetabulum. The capsule of the joint, a portion of the ilium and the trochanter were exposed by an incision running from the anterosuperior portion of the spine to 2 cm. below the top of the trochanter and then backward and upward. A broad long slot was made through the outer and inner tables of the ilium just above the head of the femur, and a thick graft removed from the trochanter and upper portion of the shaft of the femur was placed horizontally in the slot. A square piece of

47 Pendergrass, E. P., Gilman, R. L., and Castleton, K. B. *Am. J. Roentgenol.* **24**: 234, 1930.

48 McEvedy, P. *Lancet* **2**: 902 (Oct. 25) 1930.

49 Campbell, W. C. *Surg. Gynec. Obst.* **51**: 381, 1930.

50 Soutter, R. *Surg. Gynec. Obst.* **51**: 249, 1930.

bone cut from the outer table of the ilium above the acetabulum was lowered and brought into contact with the femoral graft, the lower edge being held with catgut stitches

This procedure had been used successfully in 9 cases by Soutter during the last three years in patients ranging from 6 to 18 years of age

[ED NOTE—The technic is neat and constructs a prop to prevent upward tilting of the bony shelf]

Extra-Articular Arthrodesis of the Hip—Mathieu⁵¹ had performed extra-articular arthrodesis of the hip in 21 cases by the following technic. The patients were placed on an orthopedic table with the leg abducted. The Smith-Petersen incision was used. The greater trochanter was sectioned. A flap of the ilium was turned down so as to reach the cut edge of the trochanter. The freed trochanter was then slid on to the wing of the ilium and fixed with screws or nails. A plaster was applied for three months. The indications for the operation were (1) painful forms of chronic arthritis, (2) unstable hips (3) hips incompletely ankylosed with progress toward deformity

Operative Treatment of Lesions of the Lower Extremity in Diabetes Mellitus—McKittrick and Pratt⁵² reviewed 281 operations on the lower extremity in patients with diabetes mellitus. They found it helpful to divide the lesions into those due to arterial insufficiency and those due primarily to infection. *Staphylococcus albus* was the organism most frequently encountered in infections of the feet. Gas bacillus infection was present in a single case. In the cases of circulatory insufficiency not requiring amputation, the passive exercises of Buerger were found helpful in stimulating circulation. Spinal anesthesia was the preferred form. The authors discussed the indications and methods of drainage or amputation. The mortality in these cases was 16.6 per cent.

Surgery of the Knee Joint—Henderson's⁵³ article was based on a review of 256 cases of injury to the semilunar cartilages in which operation was performed at the Mayo Clinic. There were 234 cases of injury to the internal semilunar cartilage and 22 of derangement of the external semilunar cartilage. End-results were obtained in 238 of the 256 patients, 77 per cent were relieved from all trouble, 14 per cent were improved and 9 per cent were not benefited. The results from removal of the internal semilunar cartilage were slightly better than those following excision of the external cartilage. In the series there were 42 cases in which the pathologic process demonstrated at the time of operation was not sufficient to account for the patient's symptoms, of 35 patients

51 Mathieu P. *Presse med* 38 165, 1930

52 McKittrick L. S., and Pratt T. C. *Operative Treatment of Lesions of the Lower Extremities in Diabetes Mellitus*. *Arch Surg* 21 555 (Oct) 1930

53 Henderson M. S. *Surg Gynec Obst* 51 720 1930

in this series, 13 were cured, 8 were improved and 14 were unimproved by the removal of one or the other cartilage. The diagnosis, operative technic and postoperative care were thoroughly discussed.

FRACTURES

Nonunion in Fractures—Albee⁵⁴ stated that the chief causes of nonunion in fractures were (1) failure of granulation tissue to bridge the gap, (2) a scar formed by granulation tissue before the osseous tissue had been established, (3) too early mobilization, (4) rough manipulation of soft callus, (5) interference with circulation at the site of fracture, (6) infection, (7) steel plates, (8) absorption of solid callus before the restoration of trabecular alignment. He pointed out that fractures in elderly persons united almost as readily as those in younger adults, but that intra-uterine fractures were the most difficult to treat.

The methods of nonoperative treatment were discussed, such as diet, artificial light and various means of stimulating the fracture site locally, none of which had been wholly successful. Albee believed that there was only one successful way of treating nonunion of fractures, and that was by open operation and the massive bone graft. Motor driven instruments were considered essential, and absolute fixation of the part for a minimum of eight weeks was necessary. The graft was usually taken from the sound tibia although the sliding graft sometimes sufficed. Various types of graft and the method of fixation of the graft were discussed. A review of cases was appended.

Dorrance⁵⁵ said that osteoperiosteal grafts were indicated in selected cases of nonunion. He based his conclusion on observations, both clinical and experimental. The ideal conditions for successful results were: The osteoperiosteal graft should contain a good supply of bone with the periosteum. Periosteum that was stripped from the bone would not produce bone. One must be just as careful to fasten the graft to the bones as in the case of full thickness grafts. The same care must be used in preparing the bed for reception of the graft as in full thickness grafts. It required a longer time for the osteoperiosteal graft to become solid than for a full thickness graft. In all bone grafts one should secure as complete immobilization as possible during the first two months. The thickness and strength of the graft depended on the amount of weight-bearing that was to be required.

Fractures of the Cervical Vertebrae—Le Fevre and Jackson⁵⁶ presented their method of fixation and support of the head in fractures

54 Albee, F. H. *Surg. Gynec. Obst.* **51**: 289, 1930.

55 Dorrance, G. M. *Ann. Surg.* **92**: 161, 1930.

56 Le Fevre, L., and Jackson, S. *Fixation and Support of the Head in Fracture of the Cervical Vertebrae*, *J. A. M. A.* **95**: 1669 (Nov. 29) 1930.

of the cervical vertebrae. The apparatus consisted of two hinged ovals of irons joined together with turnbuckles. The ovals were fitted, one to the curve of the body around the neck under the chin, and the other around the base of the neck and over the shoulders. The turnbuckles allowed for adjustments or traction.

Fractures of the Acetabulum—Cubbins, Conley and Callahan⁵⁷ classified fractures of the acetabulum as follows: (1) fracture of the rim, (2) fractures involving one or two of the bones making up the acetabulum, (3) perforating fractures, and (4) extensive fractures involving all the bones making up the acetabular cup.

Treatment was based on the type of deformity. Longitudinal traction alone might suffice. If the head was centrally dislocated, a combination of lateral and longitudinal traction should be tried. A screw placed in the trochanter and into the neck was advocated as a means of gaining effective lateral traction. If the femoral head was centrally dislocated and locked, open operation offered the only hope for restoration of the normal joint.

Separation of the Lesser Femoral Trochanter—Lapidus⁵⁸ reported 2 cases of separation of the lesser femoral trochanter, one with bony separation as shown by roentgenograms and the other with probably a partial rupture of the tendinous fibers of the iliopsoas muscle. These cases were rare, occurring mostly in boys between the ages of 13 and 17 as a result of sudden overexertion of the iliopsoas muscle, usually during running. The symptoms were pain and tenderness over the lesser trochanter and weakness or complete loss of flexion of the thigh. Treatment consisted of rest in bed with relaxation of the iliopsoas muscle by means of a plaster spica applied with the hip in flexion, external rotation and adduction. Complete recovery could usually be expected.

Fractures of the Femoral Neck—Reggio⁵⁹ reporting study of patients with fractures of the neck of the femur treated at the Massachusetts General Hospital, said that he in no way attempted to voice an opinion in regard to the advantages of any form of treatment. He merely observed the end-results in consecutive cases in which closed methods had been used. No case had been omitted, thus all selection had been avoided. Forty-nine patients were treated by the Whitman method, 13 died, 18 showed good results, 5 fair results, 7 poor results, and in 6 the outcome was unknown. Twenty-one patients were treated by other methods, 5 died, 4 had good results, 2 fair results, 5 poor

57 Cubbins, W. R., Conley, A. H., and Callahan, J. J. *Surg. Gynec. Obst.* 51: 387, 1930.

58 Lapidus, P. W. *J. Bone & Joint Surg.* 12: 548, 1930.

59 Reggio, A. W. *J. Bone & Joint Surg.* 12: 819, 1930.

results, and in 5 the results were unknown. Therefore, "good" results were obtained in 60 per cent of the cases treated by the Whitman method, as against 36.4 per cent treated by other methods.

Santos⁶⁰ made a careful study of the changes in the femoral heads in 15 cases after complete intrascapular fracture of the neck of the femur. He found that the life of the proximal fragment depended on the circulation through the ligamentum teres. The vessels in the ligamentum teres were more abundant in young persons, but were adequate in many elderly persons. Bony union occurred in most cases in which the head remained alive, and there was adequate reduction and fixation. Even in the presence of necrosis of the proximal fragment, union might take place with efficient reduction or impaction followed by immobilization. Weight-bearing should be avoided until repair of the head is completed. The replacement of the dead bone took place by invasion of newly formed tissue from the round ligament and by vascularization through adhesions formed between the capsule and the eroded surface of the fracture. It was usually possible to determine from roentgenograms in from six to ten weeks whether the head was dead or alive. Where the head was alive it would show the same amount of atrophy during immobilization as the distal fragment. In case of necrosis of the head it would show greater density than the distal fragment, since it could not show bony atrophy if its blood supply were destroyed. When there is non-union and necrosis of the femoral head, a reconstruction operation should be performed. Where there is nonunion and the head of the femur remains alive, the fixation of the fracture with a bone peg is indicated if the general condition of the patient is good.

[ED. NOTE—These observations made in Phemister's Clinic are worthy of serious consideration and offer a rational basis for the selection of proper methods of treatment in patients with delayed union of the femoral neck.]

Fractures of the Femoral Shaft—Eve⁶¹ stated that open reduction should be performed in fractures of the shaft of the femur only when conservative treatment failed. One-fourth contact of the ends of the fracture was sufficient, and many good functional results were observed when overriding was present. For the upper third of the femur the author preferred suspension and traction since most of the fractures in this region were oblique. He found that 70 per cent of the fractures in the middle third of the femur were transverse. Here he used a plaster spica cast in selected cases. The cast was shortened to the knee in three or four weeks. In the other fractures of the middle third of

60 Santos, J. V. Changes in Head of Femur After Complete Intrascapular Fracture of Neck, *Arch. Surg.* **21**: 470 (Sept.) 1930.

61 Eve, D. *South. M. J.* **23**: 813, 1930.

the femur he used traction with the posterior surface of the thigh well padded to prevent backward bowing at the site of fracture. In the lower third of the femur he found the backward displacement of the lower fragment the most difficult feature. Here he advised the use of skeletal traction with a pin through the femoral condyles and with the knee flexed almost to a right angle.

Fractures of the Patella—Leavitt⁶² suggested the use of free strips of fascia about $1\frac{1}{2}$ to 2 inches (3.8 to 5 cm) wide for fixation of the patellar fragments, these being attached to the quadriceps tendon for a distance of $1\frac{1}{2}$ inches above the patella and also to the patellar tendon for the same distance below it. The edges were sutured to the tendon and the periosteum with interrupted fine plain catgut. The use of these wide and long strips of fascia gave a large area of adhesion and a consequent increase in strength.

This method was first used in 1926 in three patients who had been operated on before, and in whom the patella was again fractured. There had been no recurrences in these cases, and the patients operated on subsequent to 1926 had had no complications or setbacks.

Traction Apparatus for Naval Vessels—Shaar⁶³ had made an addition to the usual overhead traction and suspension frame whereby jar and pendulum motion of the weights was prevented in hospital ships. This addition consisted of a steel tube through which the cords passed to the weights. The tube could be attached at any angle and at any height. Swaying of the weights was prevented.

DISLOCATIONS

Habitual Dislocation of the Shoulder—Henderson⁶⁴ reported forty operations on 37 patients with habitual dislocation of the shoulder. Anterior capsulorrhaphy performed on 16 patients for anterior recurring dislocation resulted in cure in 37.5 per cent, all of these operations being done more than ten years before. Three patients who underwent posterior capsulorrhaphy for posterior dislocation remained well. Of 8 patients who underwent Claremont operations more than five years before, 50 per cent were cured. Tenosuspension performed on 10 patients had resulted in cure in 100 per cent of the cases: in 2 cases lasting for more than five years after operation, in 2 for more than three years, in 1 for more than two years, in 2 for more than one year, in 2 for more than eight months and in 1 for more than six months. The success of the operation of tenosuspension depended on the careful placing

62 Leavitt P. H. *New England J. Med.* 203:728, 1930.

63 Shaar C. M. *U. S. Nav. M. Bull.* 28:718, 1930.

64 Henderson M. S. *Habitual Dislocation of the Shoulder*. *I. A. M. A.* 95:1653 (Nov. 29) 1930.

of the strong piece of the tendon of the peroneus longus muscle to act as a suspension ligament through drill holes in the acromion process and the head of the humerus. Small incisions were required, and this was an important consideration in women. The operation did not require opening of the capsule of the joint.

[ED. NOTE.—Henderson's study has gone a long way toward solving the problem of habitual dislocation of the shoulder. Suspension with fascia is less strong than that with tendon. One of us has had recurrences following the use of fascia alone.]

Repair of Bone—Phemister⁶⁵ stated that aseptic necrotic bone in continuity with living bone was gradually invaded and more or less completely replaced by new bone through the process of creeping substitution, unless it was too inaccessible and was broken down by traumatism. In Koehler's, Kienbock's and Legg-Perthes' disease there was marked fibroblastic and fixed tissue phagocytic reaction and, in rare cases, an infiltrative reaction which resulted in absorption of necrotic bone without bony replacement by creeping substitution except in occasional instances. New bone formed from surviving osteogenic elements replaced the absorptive tissues more or less completely in the course of time. Histologically the majority of these lesions appeared to have something more back of them than a simple bland embolus or injury cutting off the circulation and producing aseptic necrosis.

From work based on the histologic study of a series of experimental fractures produced in rabbits Ham⁶⁶ made the following summary:

"The adult bone cell is distinguished from the osteogenic cell which is found lining the bone in the periosteum, the Haversian canals and the endosteum. The osteogenic bone cells proliferate and differentiate into bone and cartilage. The usual method of bone repair is through the agency of these specific osteogenic cells and not by the metaplasia of fibroblasts."

Two factors, the presence of a local deposit of calcium salt and a good blood supply, were of great importance in effecting the differentiation of the osteogenic cell into bone. Cartilage resulted from the growth of osteogenic cells in the absence of these two factors.

Reaction of the Joints to Foreign Bodies—Moulouguet and Mihailescu⁶⁷ studied the fate of fragments of bone introduced into the synovial cavities of rabbits by pulverizing bone and injecting the powder into the joints. In five days many of the fragments were included in the synovial membrane. In ten days all were surrounded by synovial cells and excluded from the joint. There were many macrophages. Changes

65 Phemister, D. B. *J. Bone & Joint Surg.* **12**: 769, 1930.

66 Ham, A. W. *J. Bone & Joint Surg.* **12**: 827, 1930.

67 Moulouguet, P., and Mihailescu, G. *Presse med.* **38**: 453, 1930.

could be seen in some of the bony fragments. It seemed apparent that the greater part of the fragments were destined to be completely destroyed by osteoclasia or osteolysis and to disappear without damage to the joint. However, when the fragments were introduced by arthrotomy, there was a constructive reaction about some of the fragments, leading to the formation of osteophytes.

Structure and Function of Articular Synovial Membranes—Sigurdson⁶⁸ studied the structure and function of articular synovial membranes, using the joints of the guinea-pig, rabbit, cat, dog, human fetus and adult. His conclusions were:

1 The inner surface of articular capsules is not formed by a distinct membrane, but by connective tissue modified as the synovial surface is reached.

2 The superficial synovial cells are not uniform in size or shape, some being quite small and round, while others are large with branching processes.

3 Synovial villi vary greatly in size and shape, and are composed of connective tissue resembling the part of the capsule from which they arise.

4 An excellent demonstration of variation in cell outlines on the synovial surfaces of articular capsules can be obtained by the use of silver-impregnation methods. The intercellular substance is found to be abundant in contrast to that of the pleura and peritoneum, and the apparent cell outlines are much more irregular and do not resemble those of an endothelial or mesothelial layer.

5 The presence of "stomata" in articular capsules is not confirmed.

6 Carbon particles, when injected into knee joints of guinea-pigs, evoke an inflammatory exudate in the joint cavity most marked on the third day after injection. Some of these carbon particles are taken up by the lymphatic vessels and are deposited in the inguinal and lumbar nodes, while others are removed from the joint cavity by the action of phagocytic cells, some of which gain the lymphatic vessels, while others remain in the subsynovial connective tissue for an indefinite period.

7 Iron, in the form of ferric ammonium sulphate, disappears from the joint cavities within thirty minutes after injection by way of the lymphatics.

8 Iodine, in the form of lipiodol, diffuses slowly through the joint capsule, a period of at least four days being required for its complete removal as judged by skiagrams.

9 Immobilization of the tibio-tarsal joints in rabbits over fifty-three days produced no marked structural changes in the joint capsule, but the amount of synovial fluid was considerably less.

Synovial Fluid in Infections and Neuropathic Arthritis—Shands⁶⁹ reported the changes in the synovial fluid in 123 cases of inflammation of the joints. In 105 cases of chronic infectious arthritis bacteria were recovered from the synovial fluid in 38.1 per cent. These bacteria were chiefly nonhemolytic streptococci. The cell counts and the percentage of polymorphonuclear cells were higher in the joints in which positive

68 Sigurdson, L. A. J. Bone & Joint Surg. 12: 603, 1930.

69 Shands, A. R. South. M. J. 23: 818, 1930.

cultures were obtained. The average count of cells was 8,109 per cubic millimeter when cultures were obtained and 5,144 per cubic millimeter when cultures were not obtained. There were 4 cases of acute, gonorrheal arthritis in 3 of which the gonococcus was recovered. The cell counts in these cases were higher than in the group of infectious arthritis. There were 4 cases of traumatic synovitis in which the swelling of the joint appeared several days after injury. Bacteria were recovered in 2 of these cases. In these the average cell count was 8,200. The synovial fluid was examined in ten neuropathic joints. Organisms were obtained in 4 cases. In 3 cases *Streptococcus viridans* was recovered, and in the fourth case *Staphylococcus aureus*. The average cell count in these cases was 3,200 with 57.7 per cent polymorphonuclears.

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